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REGULAR DEPARTMENTS

A. M. A.
Archives of Neurology and Psychiatry

VOLUME 80 JULY 1958 NUMBER 1

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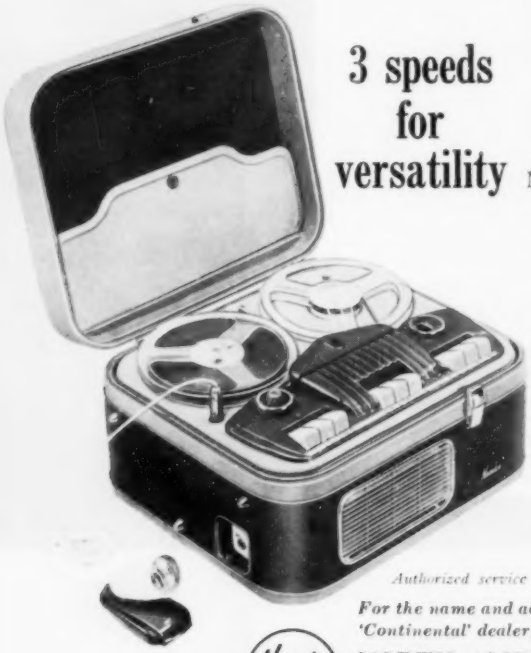

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AGITATION IMPEDING PSYCHOTHERAPY. When first seen, this patient was markedly agitated and destructively aggressive. Her excitation was a barrier to psychotherapy. Response to SPARINE: The hyperactivity gave way quickly to emotional calm, and rapport became established.

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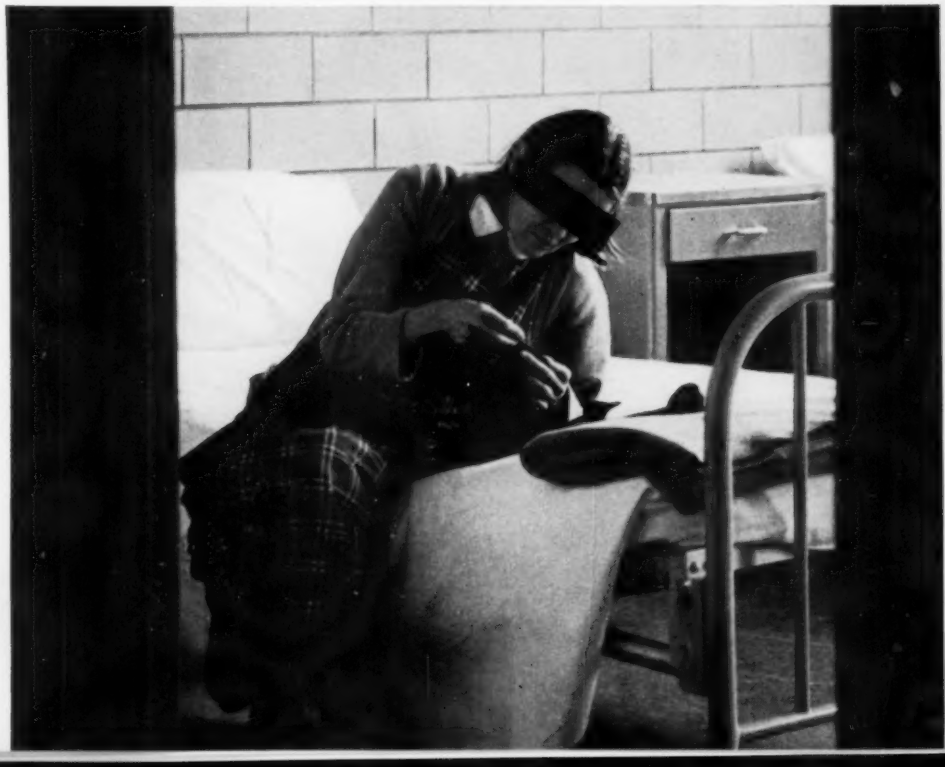

ENILE AGITATION. This is a nursing-home patient with erebral arteriosclerosis. Like many such patients, she was hostile, ssaultive, acutely restless, and untidy. Response to SPARINE: he quickly became calm, relaxed, and improved in interpersonal elationships. She has resumed a normal interest in personal ygiene and appearance.

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1. Bowes, H. A.: Am. J. Psychiat. *113*:530 (Dec.) 1956.
2. Bruckman, N., *et al.*: Am. J. Psychiat. *114*:262 (Oct.) 1957
3. MacGregor, J. M.: South African M. J. *30*:1108 (Nov. 17) 1956. 4. Sarwer-Foner, G. J., and Koranyi, E. K.: Canad. M. A. J. 77:450 (Sept. 1) 1957.

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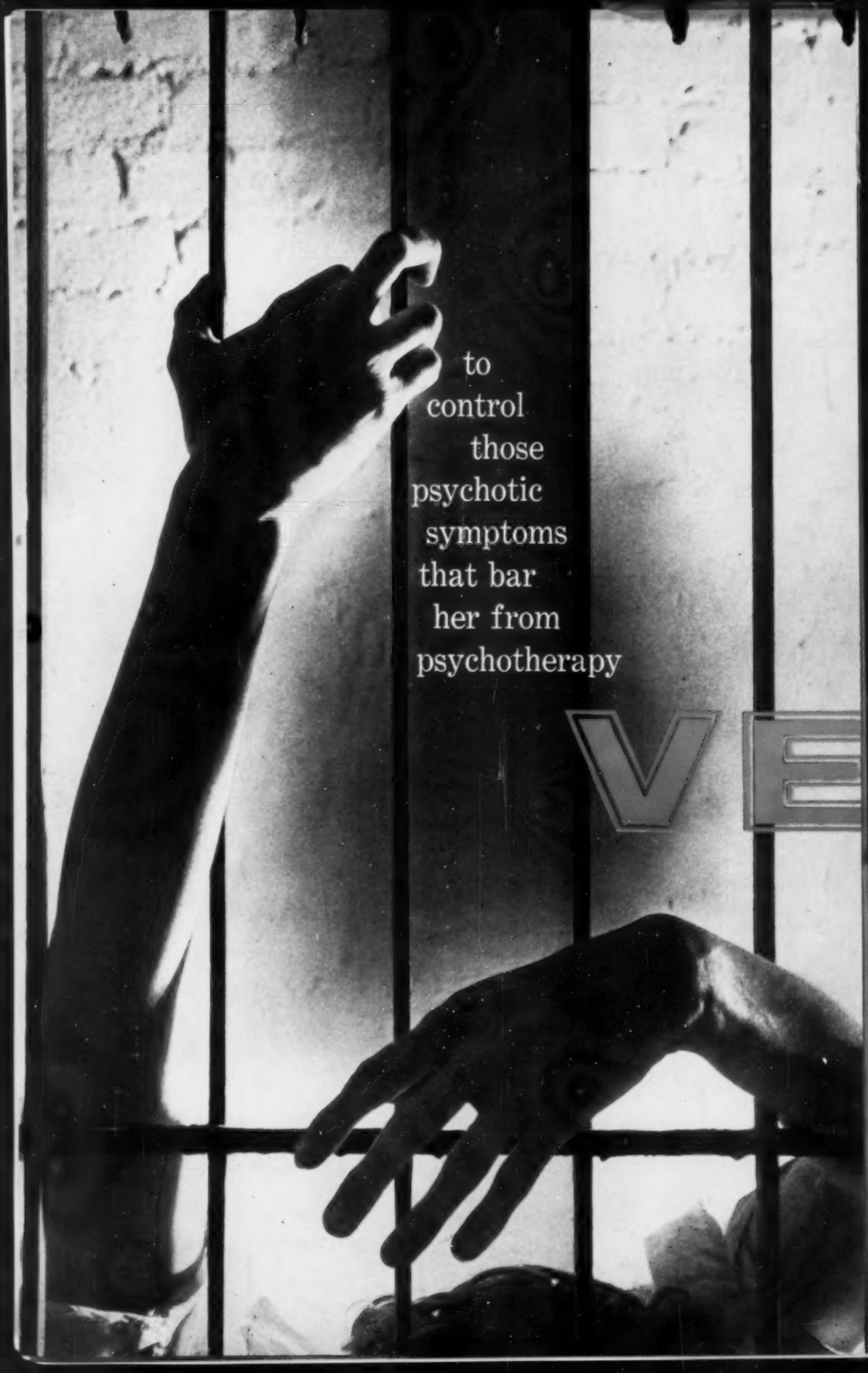
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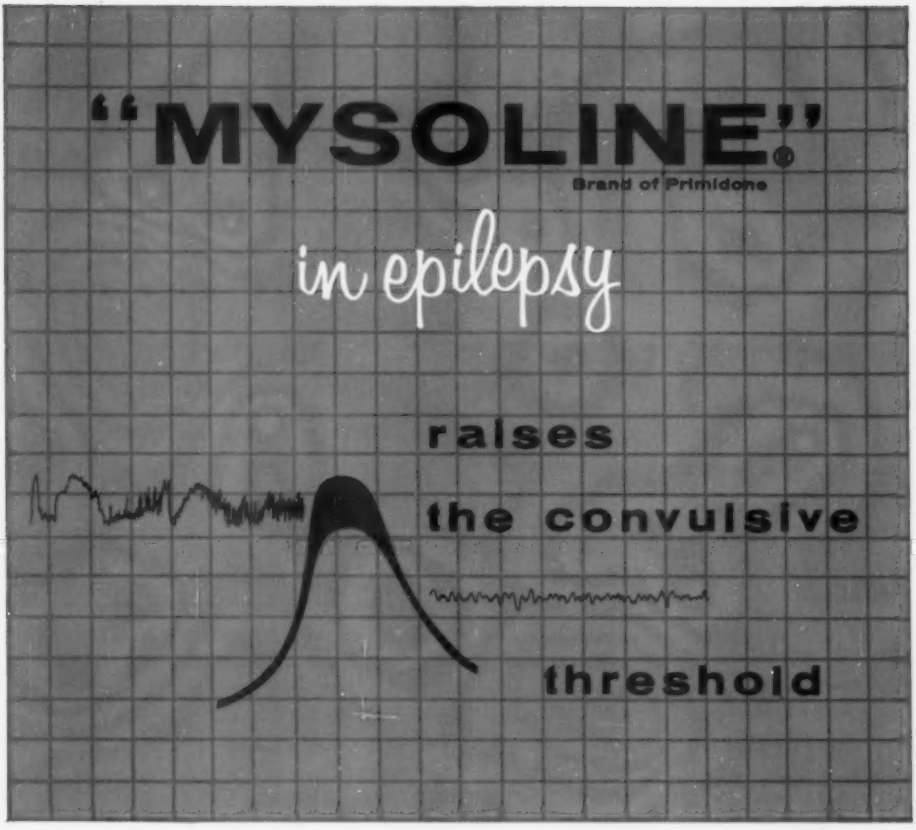

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1. Graffagnino, P. N., Friel, P. B. and Zeller, W. W.: Emotional disorders treated with meprobamate and promazine. Connecticut M. J. 21:1047, Dec. 1957.

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(hospitalized patients—all types)

by disease

DIAGNOSIS	NO. OF PATIENTS	NO. IMPROVED
SCHIZOPHRENIA		
PARANOID	7	2
NON-PARANOID	45	34
DEPRESSION		
PSYCHOTIC†	37	25
NEUROTIC	16	10
ANXIETY STATE	9	8
CHARACTER DISORDERS	15	13
OTHERS	16	13
TOTALS	145	105

by symptom

SYMPTOM	NO. IMPROVED
SLEEP DISTURBANCES	36
ANXIETY	30
TENSION	31
AGITATION	8
OTHERS	11
TOTAL	116

†Relief mainly in symptoms of anxiety, tension and insomnia.

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Paramyotonia Congenita

GLENN A. DRAGER, M.D.; JAMES F. HAMMILL, M.D., and G. MILTON SHY, M.D., Bethesda, Md.

Considerable controversy exists in the literature regarding many aspects of myotonia, in particular paramyotonia congenita. Eulenberg [1] originally described paramyotonia as a distinct syndrome. Since the original description, some authors have placed paramyotonia under the heading of neurosis, while others include it as a variant of myotonia congenita (Thomsen's disease).

Paramyotonia is a relatively rare disorder, and only two pedigrees of the disease in the United States are to be found in the literature.[2-4] An additional pedigree, with 30 affected members, is presented, with a review of the literature and clarification of the characteristics of this disorder. The clinical and anatomical pathology will be discussed.

The Syndrome

A clinical syndrome must have singular characteristics, positive and negative, by which it can be identified and which are consistent. Dystrophia myotonica is considered, by some, a generic syndrome, and the establishment of separate clinical entities for the few patients who demonstrate myotonia congenita or paramyotonia is not warranted. Features warranting delineation of Eulenberg's [1] paramyotonia as a specific syndrome, however, have been known since its first descriptions. These features are well illustrated by the current cases and family study.

1. A pattern of single autosomal dominant gene inheritance with complete or near-complete penetrance, which therefore never appears as a recessive trait. Once the parent or parents appear without the trait, it does not then reappear in successive offspring (myotonia congenita and dystrophia myotonica).

2. The condition is nonprogressive, both as to myotonic phenomena and as to weakness (myotonia congenita and dystrophia myotonica). The patients actually improve with the progress of adulthood, as evidenced by the case histories showing gradual adaptability of the patients into their teens and adult life.

3. Muscle wasting is not present (dystrophia myotonica).

4. Muscle "hypertrophy" generally does not occur (myotonia congenita).

5. The myotonia is of two types: mechanical—usually lingual only and at any temperature—and reflex. The distribution of the latter is mainly facial, pharyngeal, and of the distal extremities. It is precipitated by cooling and is relieved by warming.

6. Weakness is mainly in the proximal muscles, is flaccid in type, and may be precipitated with or without cold. Relief of flaccid weakness is usually spontaneous after a period of time, although repeated activity and warming may hasten the recovery

Received for publication June 19, 1957.

From the Department of Health, Education, and Welfare, National Institutes of Health, National Institute of Neurological Diseases and Blindness, Medical Neurology Branch, Bethesda, Md.; and Walter Reed Army Medical Center, Washington, D. C.

process. Duration of weakness has been from minutes to over 24 hours. Periods of weakness may occur in the absence of myotonia.

7. Among the associated phenomena is vague upper gastrointestinal distress accompanying the onset of myotonic symptoms, in one case. Emotional lability may be a premonition.

8. Among the negative associated phenomena is the absence of clinical or laboratory evidence of endocrine imbalance other than potassium fluctuation, and the absence of visual difficulties, specifically cataract formation and of mental changes. Reflexes may be present during periods of weakness, but there is considerable diminution in the reflex response.

Genetic Study

Six generations of a family with members showing traits of paramyotonia congenita have been investigated. These six generations consist of 115 members, 30 of whom exhibit paramyotonia. Of the 30 affected members, 15 are female and 15 male (Fig. 1).

Some members of every generation are affected. Should a member of any one generation fail to show the trait, the trait then disappears from all of his or her succeeding offspring. It may be transmitted by either females or males, and both sons and daughters are affected. Every affected person has an affected parent, and the trait is present at birth and remains throughout life.

The over-all genetic picture demonstrates that the trait is a single autosomal dominant with nearly complete penetrance in this particular family. This is in agreement with the pedigrees of paramyotonic families described by Eulenberg (1896).

It is to be noted that the least affected members of a given generation have a greater tendency to give rise to unaffected offspring. The more severely affected members are more prone to give rise to affected offspring. This is illustrated by members of the fourth generation. K. X. is much less involved than H. X. K. X. has 6 children and 14 grandchildren who are not affected. On the other hand, H. X., who is more

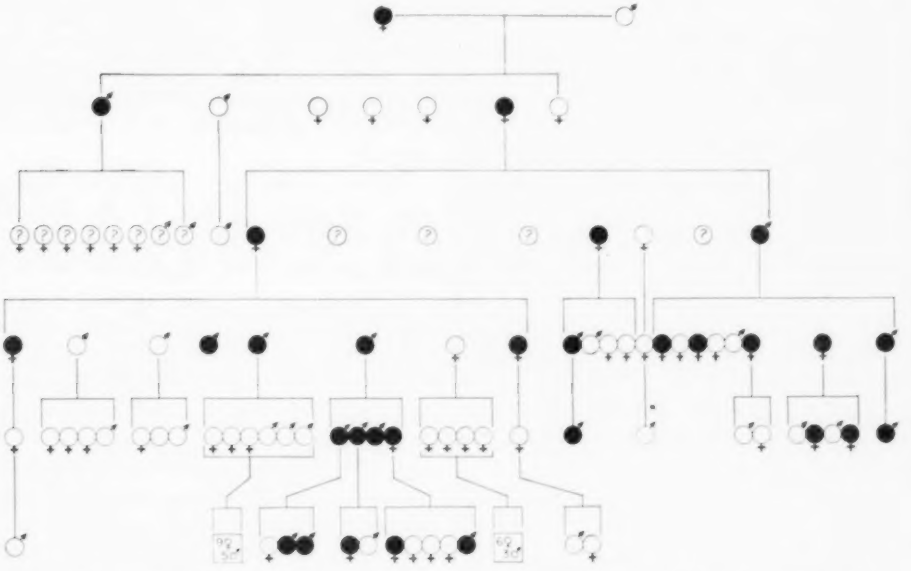

Fig. 1.—Pedigree of X. family. The black represents the members with paramyotonia. Circles with the question mark represent those members for whom paramyotonia is in question.

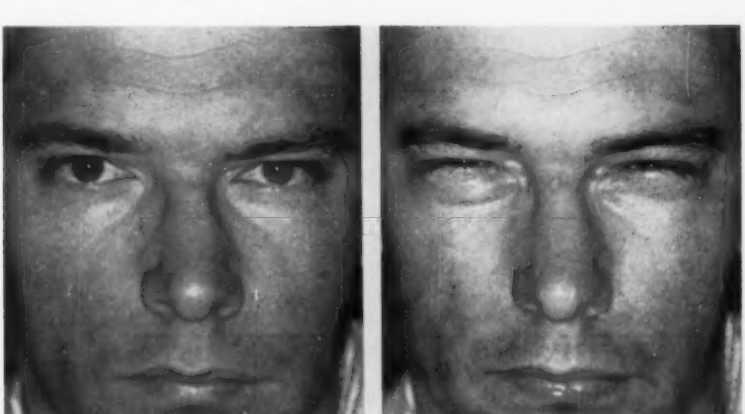

Fig. 2 (Case 1).—Effect of cold on facial muscles.

severely involved, has four affected children and four grandchildren with the trait and six grandchildren without the trait.

As far as can be determined, there is no evidence of consanguineous marriages in this family.

Four representative types of the 30 affected members of the X. pedigree are described.

Report of Cases

CASE 1 (R. X.).—This 28-year-old man has suffered from paroxysmal attacks of "cramps" and weakness since infancy. The patient differentiates two types of symptoms.

Cold-precipitated "cramps" consist of closure or partial closure of his eyelids, "freezing" of his facial musculature into an involuntary symmetrical grin (Fig. 2), and partial closure of his fist in involuntary flexion. The lids stay partially closed and his face "frozen," as though stiffened, for a period of many minutes. The hands retain their position of clenching for a like period of time. He is able to move his fingers only slightly during this time, being unable to either extend or flex them fully. He notes, however, that his fingers are flaccid at such times and can be moved passively quite easily.

The patient experiences weakness which is related to cold and which is of a variable degree—the proximal muscle groups of the extremities are most affected. Thus, he is unable to lift his knees very far upward, and consequently has particular difficulty in climbing stairs. Also, he has difficulty in raising the upper extremities. At such times he feels that the distal portions of the extremities retain normal strength. This weakness is flaccid in that his extremities can be moved passively quite easily. This proximal weakness is not preceded by any "stiffness" in the involved muscles.

Each set of symptoms may be brought on by exposure to cold. The first set of symptoms, namely, those involving the eyes, face, and hands, may result from relatively brief exposure to cold, that is, for several minutes. These symptoms then will pass off in several more minutes. The symptoms of proximal weakness, if related to temperature, result only from more prolonged chilling, which generally must last for several hours before the symptoms develop. Once developed, however, the symptoms may last for many hours. There may often be tenderness in the involved muscles once the weakness disappears. Either symptom may occur independently of the other. Exposure in cold weather, when the patient is warmly clad, will be followed by involvement only of the exposed face, eyes, and hands. The symptoms are almost always symmetrical on the two sides. However, at least once, when the patient slept in a cool room with only his left upper extremity uncovered, this extremity only was involved in an attack of the weakness.

Occasionally, not associated with the other symptoms, the patient has noted "stiffness" of his tongue, with thickness of speech after eating ice cream for several minutes or similarly cooling his mouth.

The attacks of weakness have been sufficient to incapacitate him. On one occasion he was unable to walk. Climbing upstairs is a particular effort during an attack; nevertheless, he can usually accomplish this act.

An attack of severe weakness occurred after an exposure to cold weather on the parade ground for several hours. That afternoon the patient noted mild proximal weakness of the extremities and "cramps" of the face, hands, and eyelids. The cramps disappeared on return to more temperate environment, but the mild proximal weakness of the extremities persisted. The following morning the weakness was somewhat more marked, and by the evening of the second day the patient found it quite difficult to move. The next morning, he was scarcely able to get out of bed and, once out of bed, found it impossible to walk. He was admitted to a U. S. Army Hospital, where he was found to have flaccid paralysis of the upper and lower extremities. There was no difficulty with respiration or weakness of the muscles innervated by the cranial nerves. There was spontaneous recovery of strength over an 18-hour period. The electrocardiogram and serum potassium were normal.

It was noted that attacks could not be precipitated by the forced feeding of glucose, with or without insulin, and that attacks were precipitated by whole-body immersion for 20 to 30 minutes in water at a temperature of 68 F. Flaccid paralysis of the extensors of the wrists and fingers developed. There was a lack of response of these muscles to faradic and galvanic stimulation.

On rare occasions the patient has been exposed to cold without a resultant attack of weakness. The patient is unaware of any factors involved that seem to protect him against weakness. He does note, however, that during the time he was in England with the Army he had fewer attacks than usual, despite the fact the weather was quite often cold.

The patient has no symptoms suggestive of endocrine disease.

Neurological Study.—The pertinent findings were as follows: The patient was alert, cooperative, rational, and well oriented. He was of normal intelligence. His speech was normal.

Cranial Nerves: At rest, the eyelids were normal. Upon exposure to cold water for a few minutes, there resulted a narrowing of the palpebral fissure, with depression of the upper lid and elevation of the lower lid. This partial closure was maintained for several minutes. In addition, after forced superior gaze, during which the upper lid was retracted for several seconds, there followed a marked upper-lid lag when the gaze was directed downward. This did not occur if the patient started the downward gaze from the horizontal direction, not preceded by forced superior gaze. Function of the remaining cranial nerves was likewise normal, except that there was an easily demonstrable myotonic response to percussion of the tongue.

Motor System: The volume of the musculature was normal except for possible mild atrophy of the sternal head of the pectoralis bilaterally. There were no fasciculations, no muscle tenderness, and no myotonia on direct percussion of the extremity muscles. Power of the extremity musculature was normal except for possible slight symmetrical weakness of the biceps and triceps.

Deep tendon reflexes were equal bilaterally. There was a tendency to activation of unnecessary neighboring muscle groups upon testing of individual muscles.

Sensory Status: All sensory modalities were intact.

Case 2 (H. X.).—A 61-year-old man also has had paroxysmal attacks of "cramps" and weakness since early childhood. He differs from his son (R. X., Case 1) in that the weakness may be in isolated muscles or muscle groups and may be asymmetrical, regardless of the temperature.

He can recall that on several occasions in his early years one or the other lower extremity became fixed in a flexed position while he was running. He then would fall prone. On another occasion, while jumping off a truck, the patient's lower extremities became fixed in a position of flexion at the hip and extension at the other joints of the lower extremity, whereupon he fell to the ground in this seated position.

The weakness may involve any of the movements of the extremities, but usually affects the lower extremities more frequently and more severely than the upper extremities. He has noted no predilection for either the proximal or the distal musculature. The weakness usually is apparent on his arising from bed after a night's sleep. After recognized exposure to cold, the weakness may increase over a period of several hours and then slowly subside over several hours.

The patient, also, has had attacks of profound generalized weakness. On these occasions there was practically total paralysis of all four extremities, so that the patient was bedridden and had to be turned by others. He was unable to lift his head from the bed. There was, however, no difficulty with respiration, speech, swallowing, or external ocular movements, and no ptosis. The weakness gradually disappeared in several hours. The patient has had no such attacks of this severity for the past 30 years.

Neurological Status.—The neurological examination was identical with that in Case 1 (R. X.).

Case 3.—K. X., a sibling of H. X. (Case 2), was born Oct. 4, 1893. He states that he has had what he describes as "cramps" as long as he can remember. On exposure to cold there will be a clenching and drawing of the fingers and hands. This consists of flexion in all of the fingers. Both hands are involved with about the same severity. In addition to this there will be closure of the eyelids and a "freezing" of the facial expression.

If exposure to the cold continues, his neck muscles will become extremely stiff and he is unable to move his head. Coinciding with the clenching of the hands there will be slight paralysis of the toes. He states that very seldom will movement of the ankles be involved. Occasionally, however, he has had paresis of the ankles. He states that muscles most susceptible to exposure to the cold are the muscles of the face. Often while he is working during a first cold period in the fall, suddenly his face will become paretic. He must rub his face vigorously for several minutes before the paresis passes off. However, if the cold continues, the hands and the feet become involved. If the hands do become involved, it takes at least 45 minutes of warmth to relieve the condition. The fingers become flexed and can be extended only to return immediately to the flexed position. He says that quite often while drinking cold fluids his tongue will feel stiff, his speech will be slightly dysarthric, and he will have momentary difficulty in swallowing. This passes off very rapidly. The patient, however, has on no occasion had a complete paralysis. Many times as a child he would become cold in the school room and be unable to hold a pencil; and, when called to the blackboard, he would be unable to hold the chalk. On many of these occasions he was punished by the teacher because he could not clench the chalk properly. Because of this embarrassment, he dropped out of school at an early age. Each winter he would have considerable difficulty with his hands and could not work during cold weather. Because of this, he changed occupations and has since been in the real estate and the furniture business.

Examination again revealed only myotonia of lingual muscles to percussion and hence was identical with the findings for H. X. and R. X.

CASE 4.—Y, a woman aged 62 (?), has had cramps of her facial muscles all her life. She differs from the other affected members in that she has no myotonia of the extremities but does have weakness, always related to cold.

Examination showed that she had myotonia of the tongue but no myotonia response to application of cold to the face.

Comment

Since Eulenberg [1] first described the disease paramyotonia congenita, approximately 22 families (Table 1) have been reported in the literature which in our opinion fulfill the criteria of paramyotonia congenita. The most recent reviews show the common tendency to the opinion that this disorder is a variant of myotonia congenita (Thomsen's disease [5]). If one carefully pursues Eulenberg's [1] original thesis, three criteria are apparent: (1) the presence of myotonia, which becomes worse upon cold; (2) the presence of paresis which is flail-like and flaccid, and (3) a genetic picture that is consistent with a single autosomal dominant gene, with complete, or almost complete, penetrance. A chronological list of the

TABLE 1.—*Chronological List of Families with Paramyotonia Congenita Reported in Literature*

Year	Name	No. of Cases & Generations	Myotonia		Paresis	Pathology	Genetics *
			General	Focal			
1886	Eulenberg	26/6	+ with cold	--	+	—	S. A. D.
1889	Martius and Hansemann	11/4	+ with cold	--	—	--	D.
1891	Friis cited by Thomasen		+	+	—	—	
1892	Delprat	47/5	+ with cold	--	+	+ pads	S. A. D.
1894	Rich	62/7	+ with cold	±	+	—	S. A. D.
	(1953 Stephens)		+ with cold	+	+		
1895	Hlawaczek	1/1	+	—	—	—	1 case
1895	von Sölder	(Two papers) 2/2	— with cold	+	+	--	D.
1898	Alsberg, cited by Thomasen		accomp. cold +	--	+	--	S. A. D.
1898	Funcke	1/1	Accomp. cold +	--	—	—	1 case
1916	Lewandowsky	4/3 (One detail)	Accomp. cold +	--	+	--	D.
1917	Hübner	15/4		+ myopathic facies	—	--	D.
1930	Serog	9/4	+		—	--	D.
1936	Schott, cited by Thomasen	5/2 (? Atrophy)		+ with dystrophy	—; tremor of head, nystagmus, fibrillations		D.
1938	Smitt, cited by Thomasen		+	+	—	--	D.
1943	Koch, cited by Thomasen	18/4	+	--	+	--	D.
1947	Bell	147 (Review)	+	(147 cases; review)	+	--	S. A. D.
1947	Covernton and Draper	6/3	+	--	+	--	?D.
1948	Thomasen	Review		No	Case	--	--
1954	Tschumy	13/4	+	--	+	--	S. A. D.
1956	Gamstorp	138/10	—?	--	++	+ pad	S. A. D.

* S. A. D. indicates single autosomal dominant gene; D., dominant.

families reported is seen in Table 1. Of this list, only the cases reported by Eulenberg,[1] Delprat,[6] Rich,[2] von Sölder,[7] Alsberg,[8] Koch,[9] Lewandowsky,[10] Covernton and Draper,[11] Tschumy,[4] and Gamstorp[12] fulfill the criteria of Eulenberg.[1] As the last case is presented as a new entity, it will be discussed later at some length. The cases of Martius and Hansemann,[13] Serog,[14] Schott,[15] Hübner,[16] Smitt,[17] Koch,[9] Funcke,[18] and Friis[19] did not have any evidence of paresis, and in many such cases also the disease was not transmitted as a single autosomal dominant gene. A review of Bell's[20] statistics showed a series of 173 patients with myotonia congenita, of whom 28 had normal parents. Of 147 patients with paramyotonia congenita, none had normal parents. Thus, Eulenberg's[1] original description would still hold true; i. e., if the offspring is normal, the subsequent generations will also be normal, or, to rephrase, a patient with paramyotonia congenita must always have a parent with paramyotonia congenita. Exclusive of Gamstorp's[12] family, three cases in the literature and two members of the family presented here had paresis as the only symptom; paresis is not necessarily associated with myotonia or cold. If one accepts Gamstorp's[12] disorder of adynamia episodica hereditaria as a form of this disease, the myotonia may conceivably be easily missed. In the majority of cases in the family presented here the mechanical myotonia was present only in lingual muscles and could not be obtained elsewhere in the body or from the thenar eminence. In Gamstorp's[12] pedigree only the thenar eminence was mentioned in one case; lingual musculature was not indicated as being tested. Delprat,[6] in 1892, drew attention to a family in which he felt there were two cases which resembled Thomsen's disease.[5] In this family sarcoplasmic layers were noted in muscle fibers on biopsy. This is the same pathology as has been noted by Wohlfart[21] and ourselves[22] in dystrophia myotonica. It is of interest that the same pathology was also seen at biopsy in the cases of Gamstorp.[12] It would appear that the myotonias may show this pathology in any of their various forms. It would appear that the triad originally described by Eulenberg[1] would therefore clearly differentiate this disorder from dystrophia myotonica, myotonia congenita, or myotonia acquisita. All clear cases present with both paresis and myotonia, the latter being made worse by cold, and the disease is transmitted as a single autosomal dominant gene with approximately 100% penetrance, as is true in the family discussed above. If one includes families who do not have this heredity pattern, one finds also that such families commonly have myotonia, worse upon exposure to cold, but do not have paresis. Since most forms of myotonia become worse in cold weather, it would be unfair to identify Eulenberg's[1] disease as myotonia associated with cold. The pattern of myotonia in the family reported herein, in the family described by Gamstorp,[12] and in those reported by others would seem to show that the myotonia is the least part of the illness and may be readily missed unless searched for in the lingual musculature. Both myotonia and paresis are commoner in association with cold. One could then visualize a spectrum in the myotonic disorder ranging from the universal myotonia of Thomsen's disease,[5] to the fairly localized myotonia in the thenar eminence and lingual musculature of dystrophia myotonica, to myotonia limited to the tongue in Eulenberg's[1] disease, or to the presence in both of the last two types of other characteristics of the disease with no myotonia. The presence of dystrophia myotonia without myotonia is not an uncommon finding. The other characteristic changes of the disorder allow it to be recognized even in the absence of myotonia. The same is true in Eulenberg's[1] disease. Thus, there are recorded at least three cases in which no myotonia has been found but which have episodes of paresis and in which other members of the family do have myotonia of some nature.

TABLE 2.—*Potassium Levels in Cases of Myotonia Congenita With and Without Paresis*

	Total K/Kg., mEq.	Total H_2O	Intracellular H_2O	Intracellular K, mEq.	Intrafiber H_2O	Intrafiber K, mEq.
			Case H. X.			
Before paresis						
Sample						
A	83	770	718	116		
B	84.2	776	685	123		
C	84.1	774	744	113	Ave. 700	Ave. 115
After paresis						
Sample					Ave. 556	
A	85.0	778	609	140		
B	77.6	790	614	126		Ave. 132
C	76.3	784	536	143		
			Case R. X.: No Paresis			
Sample						
A	92.9	782	666	140		
B	81.3	785	629	139		
C	98.4	776	603	163	Ave. 604	Ave. 144

As in other diseases of muscle, the relationship of serum potassium to intracellular potassium is of interest in ths particular entity. Gamstorp [12] felt that in the entity she described an attack could be precipitated by the administration of potassium. The earlier investigators, in their discussion of paramyotonia congenita, have likened it to familial periodic paralysis. In one of the two cases in which we carried out potassium studies, there seemed to be an indication that potassium did play a definite role (Table 2). Potassium levels fluctuated over a range of approximately 3 mEq. in the serum and was on the high side of normal, as in Gamstorp's [12] cases. Intracellular potassium was also calculated, as was intrafiber potassium, according to the methods of Horvath et al.[23] The findings in this particular study on biopsy specimens of muscle before and during an attack are presented in Table 2. The muscle pathology is dependent, unfortunately, upon random samplings. Thus, of 14 cases of dystrophia myotonica in which biopsy was performed at this Institute, sarcoplasmic masses were demonstrated in but 4 and ring annulates in 5. Delprat,[6] in 1892, noted the presence of sarcoplasmic masses in the disease, which he termed paramyotonia congenita. Gamstorp [12] found similar pathology in one of her cases, that of a 60-year-old man. In the two cases from this pedigree in which biopsy was done, only intracellular migration of sarcolemmal nuclei was noted, with an occasional atrophic fiber. It must be emphasized in all patients in this series that the paresis was flaccid in nature and there was no evidence of increased tone. In several members of the affected family no increase of tone was noted before the onset of paresis. In Case 1 (R. X.) the paresis was of such severity and magnitude that he was admitted to a general hospital with a diagnosis of familial periodic paralysis, at which time he was found to have had a flaccid paresis, hyporeflexia, and no signs of increased tone. Upon recovery of the attack, as in other members of the family, myotonia of the orbicularis oculi and of the tongue could be produced by the application of cold (Figs. 2 and 3). Mechanical myotonia of the tongue was present in all members of the family regardless of temperature, but universal myotonia was directly related to temperature. As in those cases described originally, striated muscle during the period of attack was refractory to both galvanic and faradic stimulation. Between attacks an increased excitability on penetration of a concentric electrode could be noted, which was characteristic of myotonia. Spontaneous activity of short duration, 2 msec. or less, and moderate amplitude could be seen to occur during paresis, as was observed in other forms of myotonia and as could be observed in Gamstorp's [12] cases. Calcium and phosphorus levels were normal in this family, as they were in Gamstorp's [12]

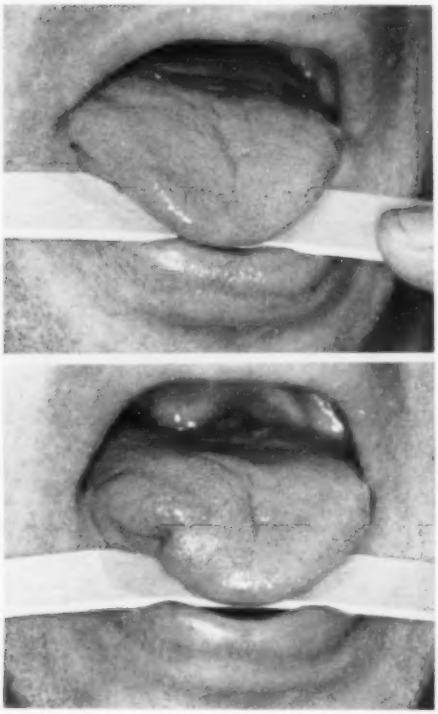

Fig. 3 (Case 1).—Percussion myotonia of the tongue.

cases, and one wonders whether the Chvostek sign which she noted was not in reality a myotonic phenomenon.

Summary

The third reported family of paramyotonia congenita in the United States is presented. A review of the literature would indicate that paramyotonia congenita is a separate clinical entity, consisting of the triad of myotonia, increasing in the presence of cold; intermittent flaccid paresis, not necessarily dependent upon cold or the presence of myotonia, and a hereditary pattern dependent upon a single autosomal dominant gene. It would appear from the review of the literature that the sarcoplasmic masses described by Wohlfart [21] were first described in a disease similar to paramyotonia congenita by Delprat,[6] and subsequently by Wohlfart [21] and in the afflicted member seen by Gamstorp [12] in a study of the disorder she termed adynamia paralytica episodica. Excessive lability of serum potassium appears to be constant in all cases reported, and a shift of intracellular potassium is not demonstrated.

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Myasthenia Gravis and Epilepsy

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Introduction

The association of myasthenia gravis and epilepsy has rarely been noted in the literature. We have been able to find only two such cases (Fearnsides, 1915,[8] and Pages and Passouant, 1953[13]). In view of the relative rarity of myasthenia gravis, the coincidence of this disease with epilepsy should be very low if based on chance only. We have, however, been impressed by the frequency with which the two conditions are present in the same patient in our experience. Eight * patients in a series of 180 cases of myasthenia gravis seen at the Presbyterian Hospital and Vanderbilt Clinic had convulsive seizures, and one additional patient had syncopal attacks without convulsive movements. It is the purpose of this paper to report the pertinent data on our cases and to discuss the possible causes of the coincidence of the two diseases.

It is difficult to determine the over-all incidence of epilepsy in the general population.[4] Selective Service statistics in the two World Wars were quoted as giving an incidence of 0.5% for men of draft age in the United States.[5,6] Alström,[1] in Sweden, in a study of the genetic aspects of epilepsy, has analyzed the family histories of 897 cases. He found an incidence of 0.9% and 0.7%, respectively, for siblings and children of epileptics at the time they were called up for military service. On the basis of these figures, an incidence of about 5% of epilepsy in our myasthenic population seems significantly high.

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* One of the patients has also been the subject of a report from another hospital.[21]

Case Material

Abstracts of the records of eight patients with unequivocal seizures are presented below. Salient findings are also summarized in the accompanying Table.

Case 1.—A woman aged 47 was first admitted to the Neurological Institute on April 19, 1946. She had noticed diplopia for 10 months prior to admission. This was followed by weakness of the right upper and, a little later, of the right lower extremity, all the symptoms fluctuating in severity. Five weeks prior to admission she first noted dysarthria and dysphagia.

Twelve years prior to admission she began having "dizzy spells" and convulsive seizures. The seizures recurred at intervals varying from 2 to 11 months. They were described as classical grand mal in type, starting with a cry, followed by loss of consciousness and tonic and clonic movements bilaterally, and ending after 5 to 15 minutes with a period of deep sleep, followed by severe headache. She had bitten her tongue at times and was usually incontinent of urine and feces. The "dizzy spells" occurred several times a day and were associated with pallor and at times with chewing movements. She did not lose consciousness in the minor spells but at times noted blurring of vision.

Neurological examination revealed weakness and fatigability of muscles supplied by cranial nerves, especially the extraocular muscles. There were marked dysphagia and dysarthria. In addition, some weakness of muscles of both legs was noted. Tendon reflexes were hyperactive, with preponderance on the left side. She had a bilateral Hoffmann sign and a Babinski sign on the right. Laboratory findings, including spinal fluid examination, were within normal limits. The electroencephalogram was normal. The pneumoencephalogram revealed mild generalized cerebral atrophy. It was considered that she might have an unlocalized brain tumor, but subsequent examination showed no progression of the pyramidal signs, which were inconstant. Of three repeated spinal fluid examinations in subsequent years, one showed a slightly elevated protein, of 66 mg. per 100 cc.; the others were normal.

She was placed on treatment with neostigmine and ephedrine and, in addition, diphenylhydantoin (Dilantin), but with only partial control of the

*Data on Eight Cases of Myasthenia Gravis with Epilepsy**

Case No.	Sex	Age at Onset		Type of Seizures and Frequency	EEG	Myasthenia Medication	Present Status	Comment
		Epilepsy	M. G.					
1	F	35	45	Grand mal †; psychomotor, 2/yr. after therapy	Normal	Neostigmine	Died 1950, 5 yr. after onset of myasthenia	Pneumoencephalogram showed symmetrical dilatation; no autopsy.
2	M	33	33	Grand mal †, irregular, 3 in 2 days	Normal	OMPA and neostigmine	Died 1952, 6 mo. after onset of myasthenia	No autopsy
3	F	14	26	Grand mal †, 3-12/yr.; none after 1950	Normal	OMPA; neostigmine; Mestinon ‡	Died 1954, 15 mo. after onset of myasthenia	No cerebral pathology at autopsy; thymectomy ineffective; sister had seizures and autopsy-proved multiple sclerosis
4	F	5	18	Grand mal †; focal motor †; psychomotor †; 0-30/day	Abnormal without specific features	Corticotropin; neostigmine; Mestinon; OMPA; W-341	Crisis 1955, age 32; survived	Thymectomy September, 1955
5	F	20	23	Grand mal †, sporadic	Normal	Corticotropin; Mestinon; neostigmine; OMPA	Crisis 1955, age 24; died 4 mo. later	Head injury age 3, with loss of consciousness of uncertain duration
6	F	34	34	Grand mal †, single seizure	Borderline	..	Not seen since 1949	Seizure occurred immediately after lumbar puncture
7	M	8	17	Nocturnal; grand mal, 1/mo.	Borderline	Neostigmine	Almost complete remission of myasthenia in past 2 yr.	Myasthenic crisis at onset
8	M	4	At birth	Grand mal, 5/yr.	Abnormal rt. occip. preponderance; atypical spike-and-wave discharge	Neostigmine	Myasthenia stationary at age 5	Motor development slow

* Ca, FBS, and BUN were normal in all patients. Skull films were also normal in all eight cases. Spinal fluid was normal in Cases 1-7; Case 8 did not have a spinal tap.
† Seizures witnessed in hospital.
‡ Pyridostigmine.

myasthenia and seizures. She had several subsequent hospital admissions, the last one in November, 1950, for lobar pneumonia, which led to a fatal exacerbation of myasthenia gravis with respiratory crisis. Permission for autopsy was not obtained.

CASE 2.—A man aged 33 was first seen in the Vanderbilt Clinic on Oct. 12, 1951, with a six-week history of ptosis, dysphagia, difficulty in chewing, and regurgitation of fluids through the nose.

His past history was difficult to evaluate. He had apparently suffered from marked general fatigue for about 11 years prior to the onset of bulbar symptoms. This was considered as due to "low blood pressure" and was treated with tonics. He had to rest for two or three hours in the afternoon after returning from work as a truck driver.

On several occasions in the past, usually at times of emotional stress, he suffered from seizures, which he was unable to describe well. He had a psychiatric discharge from the Army, following a period of violent and irrational behavior.

Neurological examination on admission revealed the bulbar signs mentioned and, in addition, some dyspnea and facial weakness. He responded initially to neostigmine but became rapidly weaker in spite of medication. He was admitted to Presbyterian Hospital and was gradually placed on octamethyl pyrophosphoramide (OMPA), with additional small amounts of neostigmine before meals. There was again improvement, with control of muscarinic side-effects by atropine.

On Jan. 7, 1952, at home, he apparently had a grand mal attack with generalized clonic movements, followed by extreme weakness and marked dyspnea. He was readmitted to the Presbyterian Hospital; OMPA was discontinued, and he was treated with neostigmine. An electroencephalogram during this admission was normal, as were other laboratory findings and x-ray studies.

His weakness was not fully controlled for the next few weeks, and he was readmitted to the hospital on Feb. 13, 1952, with an acute upper respiratory infection, excessive secretion of saliva and mucus, and dysphagia. His temperature ranged from 100.6 to 106 F. He became irrational, with paranoid ideas. Initially he responded well to antibiotics but had a sudden generalized grand mal convulsion, followed by apnea, and had to be placed in a tank respirator, after intubation. He had another generalized convulsion a few hours later and a third one the next day, in spite of phenobarbital medication. His attacks were followed by apnea on each occurrence. He died two days later. Permission for postmortem examination was not obtained.

CASE 3.—A woman aged 24 was admitted to the Neurological Institute on Jan. 30, 1953, with the chief complaints of "huskiness" of the voice, dysarthria, dysphagia, weakness of muscles of mastication, easy fatigability, and weakness of the right side of the body. These symptoms had started about two months prior to admission, at the time of an upper respiratory infection, and had become gradually worse.

Her past history was unremarkable except for the onset of convulsive seizures of grand mal type at the age of 14. She had between 3 and 12 attacks a year, usually at the time of her menstrual periods. When she was 21, she was placed on treatment with 0.4 gm. of diphenylhydantoin sodium and 0.03 gm. of phenobarbital sodium per day. She had no further seizures on this regimen.

The family history is of interest in that she had a sister suffering from multiple sclerosis (diagnosis later confirmed at autopsy) who also had epileptic seizures. An aunt and a cousin also had convulsive seizures.

Examination on admission showed marked generalized weakness and fatigability, especially in chewing, swallowing, and talking. Laboratory studies, including cerebrospinal fluid examination, electroencephalography, and roentgen studies of the chest and skull, were negative.

On neostigmine medication she had excessive secretion of saliva and bronchial mucus. Thus her myasthenia was never adequately controlled, and during several episodes of upper respiratory infection weakness was markedly increased. She reacted a little better to OMPA and was discharged on April 24, 1953.

Within 24 hours, however, great difficulty in swallowing and breathing developed. She was readmitted to the hospital and, after tracheotomy, was placed in a tank respirator.

She improved and after several weeks was able to stay out of the respirator for varying periods up to 48 hours. OMPA was withdrawn after two weeks, and her bulbar weakness was at best marginally controlled on neostigmine. In spite of large amounts of atropine and related drugs, suctioning was almost constantly necessary. She was fed by nasogastric tube and was dysarthric and often markedly dyspneic.

Thymectomy was performed on Aug. 11, 1953, in an attempt to reverse the downhill course. The operation was tolerated well; her early postoperative course appeared favorable, but no actual improvement occurred. She had again numerous episodes of myasthenic and "cholinergic" crises.

In view of her history of convulsive seizures, the anticonvulsant medication was raised to 0.5 gm. of diphenylhydantoin sodium during the pre- and early postoperative period. She had no epileptic manifestations on this medication in spite of severe repeated episodes of dyspnea and anoxia.

She was finally transferred to another hospital on Jan. 13, 1954, where she died a few weeks

later of respiratory failure. Autopsy showed no significant abnormalities of the brain.

CASE 4.—A woman aged 28 was first admitted to the Neurological Institute on Jan. 29, 1951, with a known history of a convulsive disorder since the age of 5 years and of myasthenia gravis since the age of 18.

Prior to the onset of seizures, she had fallen down a concrete step, striking her head, without loss of consciousness. This episode occurred during convalescence from measles apparently uncomplicated by encephalitis. Two days after the fall, she had the first grand mal attack, preceded by an aura of "tickling in the throat." The seizures were characterized by loss of consciousness, generalized tonic and clonic movements of all extremities, frothing at the mouth, tongue biting, and incontinence. Up to the age of 7 years she had numerous diurnal and nocturnal attacks, as many as 26 in a day. After the age of 7 the seizures gradually decreased in frequency, and during the three or four years prior to admission she had only a few grand mal attacks altogether. Ten years prior to admission, however, she began to have frequent nocturnal episodes, described as waking up with a sudden jerking movement and swinging her legs over the side of the bed. She was aware of these attacks, which lasted a few seconds. Two years prior to admission she developed additional diurnal attacks, without loss of consciousness and without falling. These attacks consisted of sudden jerking of one extremity on either side and inability to talk. These episodes lasted less than a minute.

Myasthenic symptoms first occurred at the age of 18, with ptosis of the left upper lid. She subsequently developed difficulty in swallowing, dysarthria, and generalized fatigue. On a few occasions she also had transient weakness of the legs and probably mild transient episodes of dyspnea. Seven years prior to admission, she was placed on moderately large amounts of neostigmine and was able to work in a clerical job for several years, until one month prior to admission, when weakness became markedly worse in spite of large amounts of neostigmine.

Neurological examination on admission showed ptosis, weakness of muscles of mastication, bilateral marked facial weakness, dysphagia, and dysarthria. There was no dyspnea and no major weakness of the extremities. Laboratory findings were essentially normal except for a mildly abnormal electroencephalogram both when awake and during sleep.

She had between two and eight minor seizures a day in spite of various combinations of anticonvulsant drugs. The myasthenic weakness was fairly well controlled on 150 mg. of neostigmine bromide at the time of discharge.

This patient has been followed to the time of this report. Seizures have never been controlled despite trials of all known conventional anticonvulsant drugs and of many experimental drugs. Her myasthenia has shown wide fluctuations, with many severe episodes of dyspnea, leading to tracheotomy and placement in a tank respirator during her fourth hospital admission, in April, 1955. Thymectomy was performed in September, 1955, and since then the requirement for antimyasthenic drugs has been slightly lower. She has been tried on many anticholinesterase medicaments, including OMPA, and has also had corticotropin at one time. In the late fall, 1957 she became gradually worse, had a series of severe respiratory crises and, in spite of respirator treatment, died in December, 1957. Necropsy showed no gross abnormality of the brain.

Several electroencephalograms in the past years have been mildly or moderately abnormal, without specific features or localizing signs.

CASE 5.—A woman aged 24 was admitted to the Neurological Institute on April 7, 1954, with a history of onset of myasthenia gravis in February, 1953, during the third month of her second pregnancy. Her first symptoms were dysphagia, dysarthria, and facial weakness. These were followed by diplopia and bilateral ptosis and then by marked weakness of all extremities. There was some fluctuation in severity, but her condition became worse after delivery, in August, 1953. She had a brief remission in October, 1953, then a relapse two weeks later. In January, 1954, she was placed on oral neostigmine and ephedrine, with marked initial improvement. In March, 1954, she developed dyspnea and became unable to handle secretion of saliva and mucus in spite of increase in dosage of neostigmine by mouth and parenterally.

Her past history revealed that convulsive seizures had developed in 1950, during her first pregnancy, at the age of 20. The seizures started with a sensation of weakness and choking, followed by tonic-clonic movements with loss of consciousness and tongue biting, but without incontinence, and followed by drowsiness. These seizures recurred frequently for seven months, then stopped. During the second pregnancy, she had fainting spells, lasting up to two minutes, but apparently no convulsions.

On admission she presented severe generalized myasthenia gravis with marked bulbar involvement. In spite of increasing dosage of neostigmine, her respiratory difficulties became worse, and on April 14, 1954, she had a respiratory crisis. After tracheotomy, she was placed in a tank respirator.

Subsequently, she had an extremely stormy course, with many critical episodes of respiratory failure, poor therapeutic response to neostigmine and pyridostigmine (Mestinon), marked cholinergic

side-effects, and repeated pulmonary infections, skin infections, and episodes of sinusitis. Corticotropin and cortisone failed to influence the downhill trend. She was kept in the respirator except for short periods until March, 1955, when she was placed on OMPA. On this drug, she became ambulatory and was able to stay out of the respirator for the last months of her stay at the Institute.

In February, 1955, she had two grand mal attacks on the same day. They consisted of loss of consciousness; tonic and clonic movements, lasting about one minute, and tongue biting. There was no incontinence. On another occasion she had a milder attack without loss of consciousness, characterized by irregular, jerky movements of the arms and contractions of muscles of the chest. She was placed on small amounts of phenobarbital and had no further attacks. The electroencephalogram had to be delayed until May, when she was able to stay out of the respirator. It was normal at that time.

She was discharged to another hospital, where she had a relapse, with respiratory crises, and died. Autopsy did not include the brain.

Case 6.—A woman aged 34 was admitted to the Neurological Institute on Nov. 3, 1949, with a history of muscular weakness and increased fatigability, starting in the spring of 1949. In June she noted weakness of muscles of both thenar groups, and in July she started having bilateral ptosis, diplopia, and weakness and tightness of muscles of both legs. In September she was placed on small amounts of neostigmine, with slight intitial improvement. This was followed by an exacerbation of symptoms with additional dysphagia. Her weakness was greatest in the morning and improved somewhat during the day, with an additional increase in weakness in the evening. Five days before admission she became so weak that she had to stay in bed.

There was no past history or family history of convulsive disorder. She had had one episode of "nervous breakdown" in the past, details of which are not known.

Neurological examination on admission showed normal extraocular movements but marked bilateral weakness of facial muscles and of the masseters. In addition, she showed marked generalized weakness with rapid fatiguing on repetitive movement. She also complained of dysphagia. This was borne out by a barium esophagogram.

She showed some, but not complete, relief on fairly large amounts of neostigmine. During lumbar puncture, she suddenly became unresponsive and about 15 seconds later had a brief generalized convulsion with tonic and clonic movements but without incontinence. Two electroencephalograms were essentially normal. All other laboratory findings were also normal. Her subsequent course is not known.

Case 7.—A youth aged 17 was first seen in the Vanderbilt Clinic on Aug. 22, 1952. His illness started in June, 1952, with dysphagia, dysarthria, and generalized fatigue and "lethargy." He lost about 20 lb. (9 kg.), due to inability to eat and swallow. On July 13 he had an episode of choking with cyanosis, which had subsided by the time his family physician arrived. Dysphagia became worse, and on July 15, 1952, he was admitted to another hospital with temperature of 101 F. Upon admission, he was found to have dyspnea, diplopia, ptosis, and weakness of facial muscles and of muscles supplied by the 9th, 10th, and 12th cranial nerves. Lumbar puncture was normal. He was placed in a respirator.

He had a history of nocturnal convulsive seizures since the age of 7 years. They were described as follows: He awakes, sits up, and trembles for a few moments, during which time he is unresponsive, then goes back to sleep. An electroencephalogram at another hospital was said to show a "grand mal pattern." He was placed on 0.1 gm. of methylphenylethylhydantoin (Mesantoin) five times a day and 0.1 gm. of phenobarbital sodium once a day. The seizures were reduced to about one a month.

General laboratory work-up and chest and skull films were negative. An intramuscular injection of a test dose of neostigmine methylsulfate produced dramatic relief. He was placed on oral neostigmine bromide, and the anticonvulsant medication was discontinued. He subsequently had three poorly described spells. He was discharged in July.

At Vanderbilt Clinic, three weeks later, he showed only minimal weakness of facial muscles and was placed on 30 mg. of neostigmine bromide three times a day, which appeared to control his weakness almost completely. He was also given 0.4 gm. of diphenylhydantoin sodium daily. Additional laboratory work-up was entirely negative. Repeated electroencephalographic studies were normal.

In 1954 he developed an almost complete remission from his myasthenic symptoms and required at most 2 tablets (30 mg.) of neostigmine bromide per day. The improvement has persisted to the time of writing. He continues to have occasional nocturnal seizures.

Case 8.—A boy aged 3 years was admitted to the Neurological Institute on Jan. 6, 1952. He was born at term by forceps delivery after induced labor, the second of three children.

He had difficulty in sucking and swallowing, which cleared. Soon after birth complete bilateral external ophthalmoplegia was noted. He had, in addition, bilateral ptosis and facial weakness of a varying degree, usually less marked in the

morning or following an afternoon nap. His motor development was slow; he did not sit until he was 21 months old and started walking much later. His intellectual development, on the other hand, was precocious, and he talked at the age of one year.

Neurological examination on admission revealed marked weakness of extraocular and facial muscles only. His symptoms were strikingly relieved by parenteral injection of neostigmine methylsulfate. He was partly controlled on oral neostigmine bromide, but the optimal effect did not last more than one hour.

In November, 1953, he had the first known convulsive episode, consisting of loss of consciousness, stiffening of muscles, and frothing at the mouth. An electroencephalogram subsequently showed spike-and-wave patterns. He had four additional similar seizures in the next few months.

On April 4, 1954, he was admitted to the Babies Hospital for tonsillitis. The weakness was unchanged and was limited to extraocular and facial muscles. A second electroencephalogram showed a focal abnormality in the right occipital region.

Subsequently he has been treated with pyridostigmine instead of neostigmine, with better results. He has had no additional seizures as far as known and is not now taking anticonvulsant drugs.

Relation of Myasthenia Gravis and Epilepsy

All eight patients had well-documented myasthenia gravis. All had, at one time or another, ptosis, diplopia, dysphagia, and dysarthria, and most of them also had episodes of dyspnea. The symptoms in all cases were, at least initially, relieved by neostigmine and other related drugs. Five died in myasthenic crises, between six months and sixteen years after onset of myasthenia gravis. Three patients are still alive; two are in partial remission, and one patient has not been followed.

All eight patients had grand mal epilepsy, i.e., generalized convulsions with tonic-clonic seizures. The frequency of seizures varied greatly. One had a single convulsion. Three had as many as 12 seizures a year, with marked reduction in frequency following diphenylhydantoin therapy in two. The others had sporadic seizures in bouts, at irregular intervals. Two patients (Cases 1 and 4) had psychomotor attacks in addition. One of these two (Case 4) had up to 30 attacks per day in spite of intensive treatment with a variety of anticonvulsant drugs. She also had focal motor seizures on either side without loss of consciousness and episodic arrest of speech.

It is easier to obtain a precise date of onset for seizures than one for the onset of myasthenia gravis. In two cases, however, both diseases seem to have begun at about the same time (Cases 2 and 6). In five cases epilepsy preceded the onset of myasthenia gravis by many years (Cases 1, 2, 4, 5, and 7). In the last (Case 8) myasthenia was probably present at birth, while the first seizure occurred at the age of 4 years.

None of the patients presented definite clinical evidence of organic brain disease. Mild symmetrical dilatation of the lateral ventricles was demonstrated by pneumoencephalography in one instance (Case 1). One patient had recovered from apparently uncomplicated measles when the seizures started. Another had a history of head injury with transient loss of consciousness 17 years prior to onset of seizures. One patient had a family history of seizures and verified multiple sclerosis (Case 3). On three of the patients who died autopsies were performed. The brain in two cases was essentially normal.

Electroencephalographic Findings

Electroencephalograms were performed in all cases. Six patients had normal records or only minor irregularities. One patient had moderately abnormal records on five occasions but no evidence of paroxysmal discharges, awake or during sleep. The last patient, a child of 5 years (Case 8), had spike-and-wave groups on one occasion and had, in addition, a persistent slow-wave focus over the right occipital pole.

Relation of Seizures to the Therapy for Myasthenia Gravis

Drugs used in the treatment of myasthenia gravis might conceivably have an unfavorable effect on the seizure threshold in patients subject to convulsions or might even

in themselves cause seizures in nonepileptic patients. It is therefore necessary to analyze the effects of antimyasthenic compounds in this respect.

Five patients had seizures before the onset of myasthenia. Others had seizures during remission from myasthenia gravis, when they did not require neostigmine. The myasthenia of all patients was originally treated with neostigmine; some were later changed to pyridostigmine (Mestinon). There was no evident etiological relationship between treatment with these drugs and the nature of frequency of the seizures.

Two patients (Cases 4 and 5) were treated for short periods with corticotropin, a substance considered to cause seizures in some instances. Patient 4 had many seizures daily, uncontrolled by various combinations of anticonvulsant drugs, prior to corticotropin therapy, and had the same number and types of seizures during and after this therapy. Patient 5, who was subject to sporadic seizures, had none during the short period of corticotropin therapy. The same two patients at another time were placed on octamethylpyrophosphoramide (OMPA), without any effect on the frequency of the attacks. Patient 3 received OMPA for several months without a seizure. Patient 2 had two generalized convulsions while on OMPA treatment. He was placed on neostigmine instead of OMPA and had additional seizures several weeks later.

It might be argued that anoxia is a cause of seizures, especially in patients in respiratory crises or with inadequately regulated artificial respiration. None of our patients, however, had seizures limited to this situation.

Two patients had thymectomies with no apparent effect on the seizures.

Comment

The coexistence of convulsions and myasthenia gravis in 8 of 180 patients is almost 10 times that to be expected on the basis of chance alone. This, together with the absence of any other obvious cause of seizures, naturally raises the question as to whether some metabolic disturbance related to that of myasthenia gravis is playing a part in the occurrence of seizures in these patients. The fact that six of the eight patients had normal, or nearly normal, electroencephalograms makes this question more meaningful.

Even if there is a significant relationship between myasthenia and convulsive disorders, it is difficult to explain why this association should occur. The role of acetylcholine in the transmission of impulses at both the neuromuscular junction and the central synapse has been a focal point of investigations of the pathogenesis of both disorders. However, the roles assigned to acetylcholine in these syndromes are opposite. In epilepsy there is some evidence that the seizure mechanism may involve excessive activity of acetylcholine.[2,3,7,9,12] In myasthenia, on the other hand, evidence favors the view that the acetylcholine system is impeded, either through deficient production of transmitter substance or defective response of the end-plate.[10] It is therefore difficult, on the basis of apparently mutually exclusive theories, to formulate a unitary hypothesis to explain the occurrence of both syndromes in the same patient. Much remains to be learned about acetylcholine metabolism in these disorders, however, and other possible metabolic alterations have to be elucidated.

Summary

In a group of 180 patients suffering from well-documented myasthenia gravis, 8 had, in addition, epileptic convulsions. This incidence is much higher than would be expected on the basis of chance alone. In five of these cases the seizures antedated the onset of myasthenia gravis by years.

The clinical aspects of both disorders are analyzed, and an attempt is made to correlate the findings in the hope of establishing common factors that might explain the coexistence of the two illnesses.

Neither this analysis nor a consideration of the role of acetylcholine led to a satisfactory explanation of this association.

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Tumors of the Basal Ganglia

Their Surgical Treatment

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In the medical literature there are up to the present no data available concerning the excision of primary tumors of the basal ganglia. We wish to record our experience with radical excision of some of these tumors, which was performed because palliative operations (decompressions) did not yield satisfactory results.

Pathological Anatomy

Primary tumors of the basal ganglia may have their starting point in the thalamus, the nucleus caudatus, or the nucleus lenticularis. Those starting in the thalamus are the most frequent.

Thalamic tumors are mostly intrinsic tumors of neuroglial origin. They are likely to arise in any part of the thalamus, but usually they appear to have had origin in the subependymal layer of neuroglia. There is a relation between the structure of the subependymal layer of the third ventricle and that of the tumors which occur in this area and invade the basal ganglia (Opalsky). The subependymal layer of the neuroglia is more prominent over the thalamus. It is less pronounced in the region of the tuber, at that level consisting of isolated cells, which form a real layer only in places. This may partly account for the greater incidence of primary gliomas arising in the region of the thalamus.

The internal capsule and other dense bands of white matter related to the thalamus afford a certain degree of resistance to the spread of the tumor, so that a tumor primarily growing in the thalamus remains in well-marked limits for a relatively long time (Fig. 1) and thus is sometimes favorable for successful operation. In a later stage, these tumors become progressively invasive, but generally they do not extend toward the tuber (Smyth and Stern).

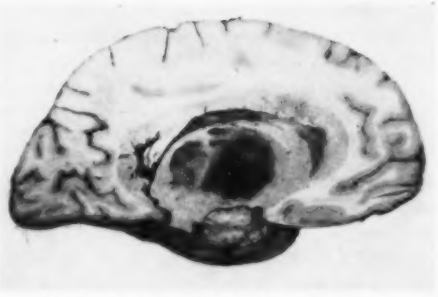

Fig. 1.—Well-delimited thalamic tumor.

Clinical Features

The symptoms of tumors of the basal ganglia require only brief description. In many cases voluminous thalamic tumors fail to induce a classic thalamic syndrome in the patient. This appears only in cases in which the neoplasm has its starting point in the ventrolateral nucleus and is destructive rather than infiltrative. Usually, tumors situated in the central part of the thalamus do not induce—in the first stage of their evolution at least—any disturbances of sensitivity, but they may sometimes produce a slight hemiparesis or cerebellar or pupillary disorder (the sign of Argyll Robertson). In summary, the clinical symptoms of thalamic tumors can be divided into two large groups, according to the part of the thala-

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mus where the most striking anatomical changes occur.

1. The tumors originating in the ventrolateral nucleus are usually inaccessible. They produce marked neurological disturbances (the thalamic syndrome of Dejerine and Roussy), as in the following case.

A 56-year-old man entered the hospital for a burning sensation, a feeling of numbness, and motor weakness of the right half of the body. The illness started two months earlier, with a continuous burning sensation in the right half of the face and in the right hand. Two weeks later he observed weakness of his right upper limb. Some days later the burning sensation spread over the entire right half of the body, and a feeling of numbness appeared in addition. Three weeks before he entered the hospital the motor weakness had spread over the whole right half of the body. Visceral examination was entirely negative. Neurological examination disclosed motor weakness in the right limbs and the right side of the face, with an increase of the deep reflexes, a decrease of abdominal reflexes, and a positive Babinski sign on the same side. There were right superficial and deep hemihypesthesia and right astereognosis. The patient felt a painful sensation when any contact was made with a large area of the right half of the body. The removal of his pajamas was painful. The feeling of continuous burning was still present. He had bilateral papilledema. On psychiatric examination only a reduction of memory and initiative was found.

An anteroposterior ventriculogram revealed moderate internal hydrocephalus, as well as a filling defect of the anterior part of the left lateral ventricle. The lateral view showed an upward displacement of the left lateral ventricle and an outline of the tumor.

Under local anesthesia, a left frontal osteoplastic flap was made. After entering the lateral ventricle, a tumor of the head of the caudate nucleus, which was also invading the thalamus, was disclosed. The tumor was brownish, had a lardaceous appearance, and was very hemorrhagic. Fragments of it (7 gm.) were extirpated.

During the operation the patient became drowsy, and after eight days, during which he remained always stuporous, he died.

Necropsy disclosed a tumor of the left basal ganglia. Microscopic examination showed that it was a glioblastoma.

2. The tumors invading the dorsomedian (medial) nucleus are more accessible. This nucleus has well-known relations with the areas of psychic activity, and the symptomatology includes mental disturbances, which are often of the type of dementia paralytica.

Among the 50 cases of primary tumors of basal ganglia which we recorded during 2000 surgical interventions performed for brain tumors in 20 years (1935-1955), there were 36 tumors of the thalamus (30 unilateral—15 right, 15 left—and 6 bilateral), 4 tumors of the nucleus caudatus, and 10 tumors situated in the nucleus caudatus, the nucleus lenticularis, and the thalamus.

The patients included 34 men and 16 women. They belonged to the following age groups: 0 to 10 years, 2; 11 to 20 years, 6; 21 to 30 years, 13; 31 to 40 years, 10; 41 to 50 years, 9; 51 to 60 years, 8, and over 60 years, 2.

The time elapsed between onset of clinical symptoms and admission to hospital in nine cases was less than one month (in one case only a week). In 25 cases, it was 6 months; in 8 cases, less than 1 year, and in 7 cases, more than 1 year (1 of them had a course of 2 years; 1, of 7 years; 1, of 10 years, and 1, as long as 15 years). One of the cases had an acute onset.

The following clinical symptoms were recorded. These were symptoms of intracranial hypertension in 68% of cases (34 out of 50). In 66% (33) of the cases there was slight hemiparesis without contracture, due to involvement of the internal capsule. Sometimes only facial paresis of central type was to be noted. In only one of the cases did marked hemiplegia develop. Pyramidal symptoms were more frequently due to tumors situated in the central part of the thalamus in the initial stage, without any disturbances of sensitivity. In 43% of our patients we noted epilepsy, 40% of whom had focal seizures, while 60% developed generalized fits. We also recorded epilepsy of the posterior diencephalic type, described by Morsier. We found psychic disturbances in 70% (35) of the cases, as compared with 83% of the patients of Smyth and Stern. These disturbances consist in a lability of attention, lack of initiative, am-

nesia, and confusional phenomena, as in the following case.

A 21-year-old man was referred to our clinic from a neurological clinic for left hemiparesis, left hemihypesthesia, and psychic disturbances. The illness started four months earlier with slowly progressive left hemiparesis. Because of his psychic disturbances, he was unable to give other details. Visceral examination disclosed no significant abnormality. Neurological examination revealed a moderate motor weakness, as well as an increase of the deep reflexes, a decrease of the abdominal reflexes, and a positive Babinski sign, all on the left side. There was a slight degree of wasting in the muscles of the left hand. He had hemihypesthesia for touch and pinprick on the left. He was unable to control his sphincters. Ophthalmoscopic examination was negative. Psychiatric examination showed indifference and apathy, with no initiative or power of introspection. Memory was very deficient. He answered only slowly; and when asked if he was aware that he urinated in his bed, he smiled and after a period answered that he was not.

Ventriculography showed on the anteroposterior view an internal hydrocephalus, with a filling defect of the floor of the body of the right lateral ventricle. The tip of the temporal horn was much dilated, so that it could be seen through the orbit. The third ventricle was not filled. On lateral view, a filling defect of the body of the right lateral ventricle could be seen to outline a thalamic tumor.

Under local anesthesia, a right frontal osteoplastic flap was made. The lateral ventricle was entered through the frontal lobe. A brownish-gray hemorrhagic tumor was disclosed in the right thalamus and was partially ablated. After the operation the patient became hemiplegic and drowsy. He did not recover and died within three weeks.

Microscopic examination showed that the tumor was a glioblastoma.

With bilateral thalamic tumor, marked dementia, hypersomnia, and a bilateral grasping reflex appeared. The cause of these psychic disturbances was not clear. Compression of the gray and white matter as a result of hydrocephalus could induce a decrease of psychic activities but was not marked in thalamic tumors associated with severe psychic disturbances. Moreover, there may be no psychic troubles in the marked hydrocephalus induced by tumors of the posterior fossa. We assume that disturbance in the interrelation of the nucleus dorsomedialis of the thalamus and the frontal cortex is more likely to cause the psychic disorders related to thalamic tumors.

The thalamic syndrome was seldom recorded in our series—in 12% of our cases only—whereas Smyth and Stern found it in 16.5% of their cases. Even when the ventral and lateral nuclei were destroyed, the thalamic syndrome was seldom complete. In one of our cases the patient had a feeling of burning in one leg as the first symptom, which lasted for one year. In another case there was pain on one side of the abdomen. Such pain was usually violent, and a feeling of burning might be continuous or might appear in attacks, which were not improved by the usual therapy. In one of the Smyth and Stern cases there was an unpleasant cold feeling in the elbow and the shoulder, and in this case the ventral and lateral nuclei were destroyed. In 20% of our cases such disturbances of sensitivity were recorded, as in the following case.

A 17-year-old youth entered the hospital complaining of motor weakness and a feeling of numbness of the left half of the body. The illness started three months earlier with bouts of vomiting. Soon afterward, slowly progressive motor weakness and a feeling of numbness appeared in the left half of the body. Visceral examination was negative, and neurological examination disclosed left hemiparesis with an increase of the deep reflexes and a positive Babinski sign. The patient presented also a left hemihypesthesia for both superficial and deep sensations and left astereognosis. The optic papillae were slightly blurred. Psychic examination revealed no pathological features.

An anteroposterior ventriculogram showed hydrocephalus without lateral displacement of the ventricular system. There was a filling defect of the right frontal horn. On the lateral view the tumor was seen to be outlined by the filling defect.

Under local anesthesia, a right frontal osteoplastic flap was made. On entering the lateral ventricle, a pale, firm, grayish, relatively well-delimited tumor was found in the anterior two-thirds of the thalamus. A complete macroscopic extirpation was made. The weight of the tumor was 22 gm. Microscopic examination showed that it was an oligodendroglioma.

After the operation the hemiparesis was more accentuated, but after six months only discrete motor weakness remained, as well as the hemi-

hypesthesia and astereognosia. X-ray treatment was not given.

These disturbances of sensitivity might be of the superficial type (tactile and thermal sensitivity), but disturbances of deep sensation were especially pronounced, associated with astereognosis. Cerebellar disorders were caused by disturbance in the functions of the cerebellar-rubrothalamic system, ataxia and hemiasynergia being noted in 48% of the cases. Vestibular disorders were slight and vague. Induction of nystagmus was normal because of the integrity of the primary reflex arc (Aubry). The Argyll Robertson pupil and paralysis of upward gaze are recorded in tumors situated in the medial part of the thalamus, but we found them in only 6% of our cases (three of the cases had the Parinaud and Argyll Robertson signs). The presence of the Argyll Robertson phenomenon may lead to an erroneous diagnosis of neurosyphilis, particularly in cases where it is associated with psychic symptoms similar to those of dementia paralytica. Homonymous hemianopsia was noted in 10 cases. The optic fundi were normal in 16 cases (32%). In 28 cases there were blurred disks; in 13 there was papilledema; in 15, florid papillary stasis. In five cases a secondary optic atrophy was disclosed at the opthalmoscopic examination. In one of the cases there was optic atrophy of the primary type. Among our cases with thalamic tumors, there was one with an adiposogenital syndrome (through compression of the hypothalamus) one with a pseudobulbar syndrome, and one case (a child) with generalized osteophytes, gynecomastia, and macrogenitosomia.

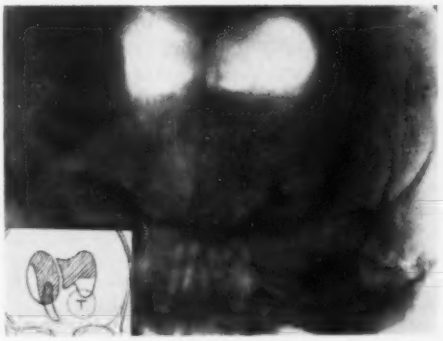

Fig. 2.—Anteroposterior ventriculogram. The interventricular septum is not displaced. Moderate bilateral frontal hydrocephalus. The inferior part of the right frontal horn shows a filling defect. The third ventricle is displaced to the left. Diagnosis: tumor of the head of the caudate nucleus on the right.

Involuntary movements (choreoathetosis, myoclonus, or Parkinson-like movements)

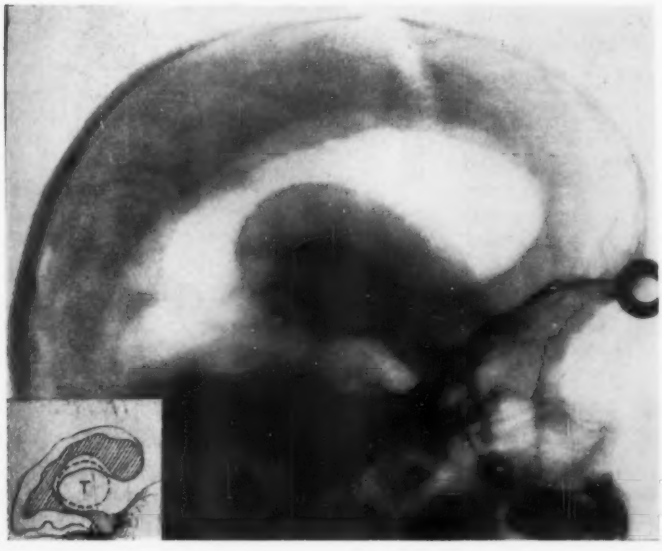

Fig. 3.—Lateral ventriculogram. The lateral ventricle opposite the tumor is hydrocephalic. The ipsilateral ventricle is displaced by the tumor.

and alterations of the muscle tonus (rigidity), presumably due to tumor involvement of the basal ganglia, or extrapyramidal system, were recorded in only 10% of our cases.

Pathological Anatomy

In our series, we recorded 15 astrocytomas, 13 glioblastomas, 15 spongioblastomas, 2 oligodendrogliomas, 1 nonclassified glioma, and 4 tuberculomas.

Radiological Features

Simple radiography of the skull showed signs of intracranial hypertension in 70% of the cases.

Ventriculography, to show the localization of the tumor, was performed in all cases. The ventriculographic features of tumors of the basal ganglia are as follows: The line of the ventricular septum is not, or is only very slightly, displaced (Fig. 2). In the anteroposterior view, there appears enlargement of the tip of the temporal horn of the lateral ventricle, which is the reason for its bulging close to the orbit (Fig. 3). In the posteroanterior view there may appear to be an enormous supraorbital cyst, as noted by Schlesinger. The absence of filling of the third ventricle and of the descending part of the temporal horn is characteristic of tumors growing in the basal ganglia.

Radiographs taken laterally may indicate very precisely the site of the tumor, by the ventricular filling defect (Fig. 3). On the radiographs taken in the anterior and lateral positions, a marked hydrocephalus of the ventricle of the side opposite the tumor is seen.

Positive diagnosis of tumor of the basal ganglia was made on the basis of neurological findings in 84% of cases and was confirmed by ventriculography.

Treatment of Tumors of Basal Ganglia

Because of their topographical position and of the important centers in this area, tumors situated at the level of the basal ganglia have hitherto not been operated upon. Up to the present, the therapy has consisted in most cases of dehydration and x-irradiation after subtemporal decompression or after a decompressive frontal flap has been made. X-ray therapy has not proved effective for brain tumors localized in the basal ganglia because of the type of such neoplasms, which are mostly astrocytomas, oligodendrogliomas, spongioblastomas, and glioblastomas, tumors which are more or less x-ray-resistant, or tuberculomas. Of 50 patients admitted between 1935 and 1955 to the Neurosurgical Clinic of Hospital No. 9 of Bucharest, 10 died during the first days of hospitalization, before being operated upon, because of their precarious general condition; 27 were subject to palliative intervention (subtemporal decompression in 15 cases, decompressive frontal flap in 12), followed by x-ray therapy. All the 27 died within a few months. Similar results are recorded in the literature.

Considering these unfavorable results, we decided to perform radical excision in such cases. We have operated upon 13 tumors of the basal ganglia. Nine of our patients are alive and four of them have died, i. e., an operative mortality of 30%. We have operated upon 10 thalamic tumors, 2 of the caudate nucleus, and 1 diffuse. Of the thalamic tumors, four were tuberculomas and six gliomas (two glioblastomas, three astrocytomas, and one oligodendroglioma); four patients died (two with tuberculomas and two with glioblastoma), and six are alive (two with tuberculomas, three with astrocytomas, and one with oligodendroglioma) and in good condition, having been operated on in 1949, 1950, 1952, 1954, and 1955 (two cases) respectively. One of the two patients with tuberculoma (25 gm.), operated upon in 1954, remained with a slight hemiparesis; one of the patients operated upon in 1952 had for one year after the operation a marked hemiplegia with a thalamic syndrome and an aphasia which subsided partly, leaving a rather pronounced hemiplegia, without aphasia. The thalamic

pain also subsided, and the patient has now resumed work.

One patient with oligodendroglioma (22 gm.) and one with astrocytoma (37 gm.), both operated upon in 1950, are in a good condition; they had developed marked hemiparesis, which improved after six months, leaving but a slight degree of paresis. No postoperative x-ray therapy was administered. In one patient with cystic astrocytoma, operated upon 18 months prior to the time of writing, only a contralateral increase in deep reflexes remains. The patient feels well, is able to go to school, and shows no further psychic disturbances. In another case, a partial excision of cystic astrocytoma of the thalamus on the left side was performed six months prior to this report; the patient, however, has a rather evident hemiplegia (which was present before the operation), but he is able to walk. The two latter patients received x-ray treatment in addition.

Two patients with tumors of the head of the nucleus caudatus, both astrocytomas, operated upon in 1949 and 1950, are in perfect health and display no neurological or psychic symptoms whatsoever, although before operation they had hemiparesis and significant psychic disturbances. None of these received postoperative x-ray therapy.

The case history of one of them follows.

A 30-year-old man entered the hospital because of headache and motor weakness in the left half of the body. The illness began two months earlier with headache. A few days later the patient observed the appearance of slowly progressive motor weakness in the left half of the body. He was not able to give other details of the evolution of his illness. Visceral examination was entirely negative. On neurological examination, discrete motor weakness in the left side of the face and the left limbs, as well an increase in the deep reflexes of the same side, was observed. There was papilledema in the right eye. He had no other neurological disturbances. On psychic examination the patient was apathetic and indifferent and did not seem to be aware of the questions put by the physician. Sometimes one had the impression that he was not even aware that there was somebody else in the room. Memory was greatly impaired.

Ventriculography showed in the anteroposterior view a moderate hydrocephalus of both frontal horns with a filling defect of the anterior and inferior portions of the right frontal horn. The interventricular septum was not displaced, but the third ventricle was pushed to the left. On the lateral view, an encroachment on the anterior and inferior portions of the right frontal horn was seen, as well as moderate internal hydrocephalus.

Under local anesthesia, a right frontal osteoplastic flap was made and the lateral ventricle entered. A tumor of the head of the caudate

Figs. 4 and 5.—Drawings showing the zone invaded by the tumor, which was extirpated.

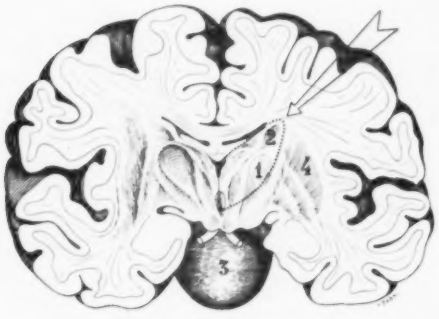

Figure 4

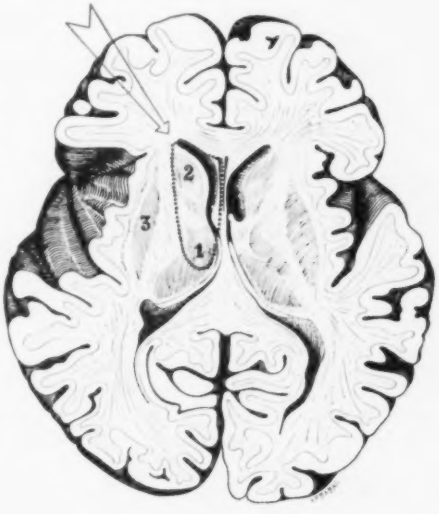

Figure 5

nucleus was found and was macroscopically entirely removed. Its weight was 22 gm. Microscopic examination showed that it was an astrocytoma of the protoplasmic type.

After a stormy postoperative course, the patient recovered rapidly. He was last seen three and a half years after operation, having no neurological sequelae or psychic disturbances. He was working in a factory.

We also present details of the other case, in which the tumor was more diffuse.

A 14-year-old youth entered the clinic complaining of headaches, nausea, and bouts of vomiting, as well as ptosis of the left eyelid. Five months before entering the hospital he began to have bouts of vomiting, headache, and nausea, which lasted for a day and appeared at intervals of three to four weeks. Three months later ptosis of the left eyelid, as well as disturbances of memory, appeared. Just before entering the clinic, he had an akinetic fit and began to present a static tremor of both hands. Visceral examination was negative. Neurological examination disclosed an increase in the deep reflexes and Oppenheim's sign on the right side. A static tremor was seen in both hands, especially on the left. In addition, he presented ptosis of the left eyelid, left internal squint, and bilaterally choked disk. There was moderate disturbance of memory.

Ventriculography showed in the anteroposterior view an internal hydrocephalus and a filling defect in the frontal horn of the left lateral ventricle, which was also displaced upward. In lateral view, the body of the left lateral ventricle was also seen to be displaced upward.

Under local anesthesia, a left frontal osteoplastic flap was made, and, after entering the lateral ventricle, a grayish, pale, firm tumor was found in the head of the caudate nucleus and the anterior half of the thalamus (Figs. 4 and 5). The tumor was macroscopically entirely ablated (25 gm.). Microscopic examination showed that it was an astrocytoma of the protoplasmic type.

These cases suggest a new therapeutic approach to tumors of the basal ganglia, which were formerly believed to be always fatal.

In patients with the less malignant tumors of the ventricular parts of the basal ganglia there are few sequelae of excision of the neoplasm, owing to the fact that neoplastic cells frequently dissociate thalamic structure without altering its components. Anatomical and functional integrity may be preserved for a long time. This accounts for cases of well-delimited gliomas or tuberculomas in which only mild disability remained after excision. The results of operation may be quite satisfactory in such cases. After operation some of the symptoms continue to improve for several (6 to 12) months, indicating that some of the lost function may be compensated, especially in children or adolescents.

When long-continued and severe compression has been present, more serious destruction of the thalamus may ensue, leading to unsatisfactory surgical results, besides providing serious immediate operative risks.

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Electrical Activity of the Hippocampus of Patients with Temporal Lobe Epilepsy

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Introduction

The electrical activity of the hippocampus and related structures in animals has been extensively investigated in recent years. Certain studies have shown that the hippocampus has a relatively lower threshold for local and propagated seizure discharges than the isocortex. Further, a high tendency of background electrical activity of the hippocampus toward synchronization has been found. The pertinent literature has been reviewed by Kaada,[13] Cadilhac,[2] and Creutzfeldt.[3] Recently, electrophysiological observations have been made on the intraventricular surface of the cornu ammonis in epileptic patients. Passouant and his associates[23] have analyzed the after-discharges of the cornu ammonis induced by electrical stimulation in 14 cases in the course of hemispherectomy or temporal lobectomy. Later, they reported on hippocampal corticography in the waking state and related the results to the histological findings in four epileptic patients treated by hemispherectomy.[25] Kellaway[16] made recordings from the scalp and the hippocampal region, using chronic depth electrodes in two patients with temporal lobe epilepsy. He found massive repetitive spike and sharp wave discharges or almost continuous abnormal activity in the depth of the hippocampus during the waking state.

Our earlier observations showed that spikes and sharp waves could be activated easily by hexobarbital N. F. (Evipal) anesthesia in patients with temporal lobe epilepsy.[14,15] Temporal pole resection or lobectomy was carried out after electrical stimulation of the lobe in more than 50 cases.[10] In seven patients sclerosis of the cornu ammonis was found on histological examination of the excised material.[9] Four of the patients stated that their first attacks appeared at night during sleep. Consequently, it was supposed that hexobarbital anesthesia might activate the hippocampal spike discharges in man. Direct electrographic explorations on the human hippocampal surface during barbiturate (hexobarbital) sleep seemed to be justified by lack of such observations in cases of temporal lobe epilepsy.

Methods and Material

Three female and three male patients with clinical and electroencephalographic evidence of temporal lobe epilepsy were explored electrographically in the course of surgical therapy. Operations were indicated because of unsuccessful medical treatment.

EEG records were obtained with an eight-channel amplifier before and after temporal pole resection with removal of the uncus and anterior hippocampus together, in the resting state, and under different levels of hexobarbital anesthesia. The bipolar technique was used except in one case, in which monopolar leads were taken with Goldman's average electrode. Sensory, motor, and speech areas were carefully mapped out, using thyratron stimulation. Flexible stainless-steel electrodes were placed directly upon the upper bank of the Sylvian fissure and on the anterior and posterior central, third frontal, and third and first temporal convolutions. Corticograms were recorded from the hippocampal and neocortical areas simultaneously.

In four cases resting corticography was followed by an incision of about 25 mm. length along the second temporal gyrus anterior to the vein of

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Labbé, and the inferior horn was opened. The incision was widened and kept open by an automatic retractor. Two electrodes were introduced through the openings and placed gently on the free hippocampal surface, one on the pes hippocampi and the other about 12 mm. posterior. Care was taken to avoid mechanical irritation of the hippocampus because mechanical stimuli, i. e., pinpricks, might induce local seizure discharges.[8] In two cases electrodes were attached to the cut surface of the hippocampus and white matter above the roof of the inferior horn and, in addition, to the anterior and posterior parts of the insula following resection of the temporal pole. Electrodes were linked in serial pairs.

Tracings were taken in the waking state and during artificial sleep induced by 1-2 gm. of hexobarbital sodium given intravenously at a rate of 25 mg. per 20-15-10 seconds, depending on individual sensitivity. The electrical activity of the hippocampus and of the neocortical areas was studied in almost all stages of deepening and lightening anesthesia. The depth of sleep was determined by analyzing the sleep waves of the frontal, central, and temporal cortices.[8] The depth of anesthesia lessened up to drowsiness spontaneously in two cases. In four cases strong acoustic and nociceptive stimuli were applied repeatedly. The patient was stimulated by calling his name loudly and was irritated by sharp, painful strokes on the soles and by pinching the skin for about two minutes; this stimulation was given two to four times. Effective recordings from the hippocampus lasted 15 to 22 minutes.

Brain materials excised were examined histologically. Serial sections were made in the frontal planes, and specimens were stained by the hematoxylin-eosin, Nissl, and Mallory glia methods.

Results

1. *Waking State.*—(*a*) The background electrical activity of the hippocampus was characterized in all cases by slow rhythms with differing morphology and with a voltage varying from 100μv to 300μv. The predominant frequencies belonged to the theta and delta bands, sometimes intermingled with faster alpha rhythms. A few short runs of regular sinusoidal theta waves appeared in one case; however, this patient, although able to cooperate, tended to doze because of the hexobarbital given for craniotomy. Some regularity of the slow rhythms was observed also in Case 1. Slow waves occurred almost continuously in four cases. Random slow and sharp waves were separated by flat phases and sometimes by short, low alpha runs, as in Case 2.

(*b*) Spontaneous spikes and sharp waves were obtained from the undamaged hippocampus in three patients. Single negative and positive discharges of 100μv to 250μv appeared in Cases 1 and 2; these were usually asynchronous, with spikes from the temporal cortex. These hippocampal spikes displayed a similarity to those observed in Cases 3 and 4 of Passouant et al.[24] In one of our cases (Case 3), however, only low, sharp waves occurred in the hippocampus, synchronous with high temporal spikes; thus, hippocampal waves seemed to be conducted potentials. No seizure discharge was found in the two cases in which hippocampal tracings were obtained only after pole resection. Convulsive activity from the hippocampus proved to be absent in the last case, since the pole and inferomedial part of the temporal lobe were infiltrated by an oligodendroglioma, which destroyed hippocampal cell layers completely. However, many spikes were recorded from the first and second temporal gyri anterior to the vein of Labbé.

2. *Effect of Various Kinds of Activation.*

(*a*) Hexobarbital anesthesia was used in all the cases. Original background activity of the hippocampus was depressed by the deepening anesthesia except for a short initial phase of increase. However, a new synchronization, with regularized sinusoidal waves, appeared at certain levels of sleep in all but the one case with oligodendroglioma mentioned above. This synchronized activity presented chiefly as 5-7-cps frequencies; besides these there were 3-4-cps rhythms and also an 8-cps component; a predominance of the delta band was found in two cases. The first short runs of well-shaped slow waves gradually formed longer trains, and finally they made up a continuous sinusoidal rhythm of 200μv to 400μv, lasting many seconds, or even almost one minute.

Hexobarbital synchronization of the hippocampus was strictly localized and was associated with certain stages of sleep; it was correlated with movements of the patient, and sometimes with convulsive activity.

This sinusoidal activity was obtained from electrodes placed on the hippocampal surface alone, from the anterior hippocampus before resection of the temporal pole in three cases, and from the posterior part after pole resection in two cases. In one of the last patients, sinusoidal activity was conducted at times into the white matter of the roof of the inferior horn, although with reduced voltage and with less regularity. Insular and neocortical areas did not participate in the hippocampal sleep synchronization, contrasting sharply with contemporaneous sleep activity of the neocortex and of the insula.

The relationship between depth of sleep and intensity of sinusoidal synchronization was carefully analyzed. Light sleep proved to be the optimal level for synchronization in four cases. Drowsiness and deep sleep were accompanied also by some weak theta or delta runs (Figs. 2 and 4). Synchronization culminated during the very deep sleep in Case 3, when a rhythm of 3 cps developed, with a relatively low voltage (50μv-100μv). The rate of hexobarbital administration was also of importance; too rapid injection retarded the hippocampal synchronization during deepening of anesthesia. The process of spontaneous awaking allowed the development of longer, more continuous, and higher sinusoidal activity than did falling asleep. Sensory stimulation seemed to have no special influence upon the development of sinusoidal waves.

It was noted in Case 2 that powerful automatic movements during light sleep were associated with sequences of sinusoidal theta waves. In this case the movements of the head caused artifacts in one of the temporal electrodes. It was observed that the appearance of sinusoidal trains coincided with the movement artifacts. This correlation was particularly traced, although for only a few seconds, when automatic movements started after a restful period. The parallelism between movements and hippocampal synchronization was proved also in the other cases.

A numerical diminution of the convulsive potentials occurred during the maximum intensity of hippocampal synchronization in three cases (Figs. 2, 4, and 6). The decrease seemed to affect mainly the discharges from the secondary focus, namely, temporal spikes in Case 1 and hippocampal ones in Case 2. This relationship was thought to be more than a result of the depth of anesthesia or a mere coincidence.

The trains of sinusoidal waves disappeared in drowsiness, or before awaking, and were replaced by short runs of fast rhythms concurrently with the desynchronization of the frontal and central cortices.

Seizure discharges showed a definite dependence on depth of sleep. On the one hand, deepening of sleep resulted in rarefaction of the spikes from the hippocampus in two cases and their disappearance for several minutes. No hippocampal spikes could be recorded during the transition stage from drowsiness to light sleep in Case 2 (Fig. 4) or under very deep sleep in Case 3 (Fig. 6). However, convulsive activity was obviously augmented by deepening sleep in Case 1. On the other hand, when anesthesia started to lighten, the number of spikes began to increase. Discharges were multiplied under light anesthesia and drowsiness, as compared with the waking state. However, convulsive activity diminished again in drowsiness or just before awaking in certain cases (Figs. 2 and 6).

The temopral cortex did not in all cases respond to hexobarbital injection. In Case 1 spikes were redoubled during drowsiness and light sleep both in progressing and in lessening depth of anesthesia. In Case 2 sleep caused a diminution of the convulsive activity (Fig. 4). In Case 3 the initial stage of sleep was accompanied by activation of spikes; however, progress in anes-

thesia caused a gradual suppression of discharges until their complete cessation (Fig. 6).

Detailed diagrams showed a contrast between the convulsive activity of the hippocampus and that of the temporal cortex. Spikes from the temporal cortex increased in deep anesthesia in Case 1, whereas hippocampal spikes were reduced. On the contrary, diminution of temporal discharges and an increase of hippocampal spikes occurred during lightening of sleep (Fig. 2). Such contrasting patterns appeared in Cases 2 and 3 (Figs. 4 and 6) exclusively under lightening of the sleep, when the hippocampus showed a great intensification of the spike activity, without an increase, or even with a decrease, of spike activity from the temporal cortex.

(*b*) Sensory stimulation was employed during very deep sleep in two cases and under deep and light sleep in one case each. Stimuli caused obvious changes in background activity, as well as in convulsive activity. Trains of sinusoidal waves disappeared from the hippocampus in a short time, and the picture gradually became similar to that of the waking state. Nevertheless, sensory stimulation elicited periods of sinusoidal activity in the flat ground line during deep sleep in one case.

Stimulation, however, exerted a particularly great influence upon the spike and sharp wave activity of the hippocampus. The number of discharges reached a fivefold increase, as compared with the waking state, and they gained also a significant increase in voltage in Case 1 (Fig. 1). The hippocampus of Case 3, which showed sharp waves conducted from the temporal cortex alone in the waking state, developed groups of rhythmic positive sharp waves of 2-cps frequency after sensory stimulation. These waves occurred only in the electrode on the posterior hippocampus, and they joined eventually in an electrical seizure of more than 20 seconds' duration (Fig. 5). Notwithstanding, they were reduced during awaking and disappeared completely during the last 30 seconds of drowsiness.

On the contrary, spikes of the temporal cortex were slightly or even not activated by sensory stimulation with the waking state.

(*c*) Electrical stimulation on the hippocampal surface was used in the waking state only in Case 2 because of technical difficulties. Thyratron stimulation was followed by a series of regularized 6-cps waves of about two seconds' duration in the hippocampus, and later by a conspicuous amplification of the background alpha activity (Fig. 3A). This response agrees essentially with the rhythmic synchronization induced by thyratron stimulation of the hippocampus of man reported on by Passouant et al.[22]

Illustrative Cases

Because of the peculiarity of the findings described above, it seemed to be of interest to present the most illustrative cases.

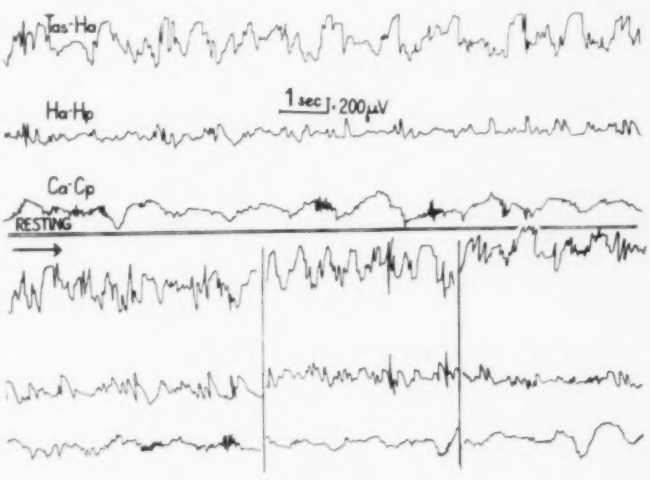
Case 1.—A man aged 32, with no family history of epilepsy or nervous disorders and no relevant past medical history, had his first epileptic attack at night in 1952. It was described as a grand mal seizure. Nocturnal fits occurred for two years but had been mixed with diurnal ones since 1954. Neither diurnal nor nocturnal seizures were preceded by warnings, but they were accompanied by complete amnesia. Diurnal seizures started with staring, paling, and hyperpnea, followed by mastication and stereotyped behavior. Postictal automatisms were noted also at night, although not frequently. Diphenylhydantoin and methylphenylethylhydantoin with barbiturate gave no therapeutic results.

Nothing abnormal was detected on neurological examination, in the cerebrospinal fluid, or in the roentgenogram of the skull. An air encephalogram was normal.

Electroencephalography revealed scanty convulsive activity in the resting state and frequent spikes in the anterior temporal region on the left under hexobarbital anesthesia. Independent spikes were picked up rarely from the homologous area on the right in hexobarbital sleep. The patient was subjected to surgical therapy on May 29, 1956 (Dr. Hullay). Since operation three seizures have occurred during the daytime. The postoperative electroencephalogram showed no convulsive potentials on the left, but some increase of temporal spike activity was found on the right under hexobarbital anesthesia.

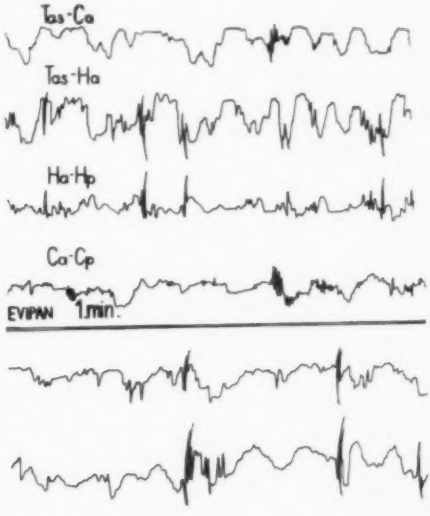
Histological study showed abnormality in the cornu ammonis only. There was loss of pyramidal cells in Sommer's sector (h_1) and a marked reduction in end-plate (Dr. Haberland). The lesion was regarded as a typical picture of sclerosis of the cornu ammonis.

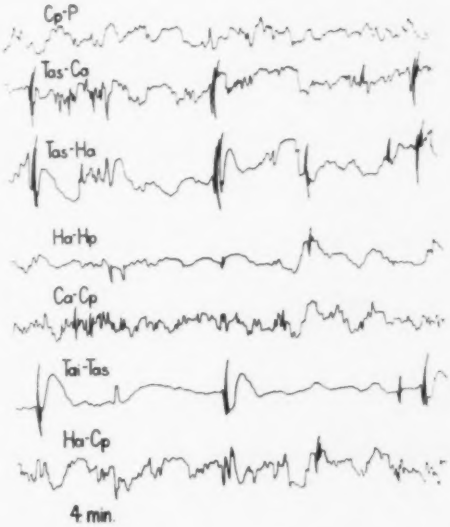
CASE 2.—A man aged 23 had suffered an injury of the right temporal region at the age of 6 years. Otherwise the previous history revealed nothing of note. The first seizure had occurred two years before, without warning signs, in the daytime. In recent months he had had fits several



Figs. 1A-1G (Case 1).—In these Figures, *Tas* indicates anterior superior temporal cortex; *Ha*, anterior hippocampus; *Hp*, posterior hippocampus; *Ca*, anterior central cortex; *Cp*, posterior central cortex; *P*, parietal cortex.

Fig. 1A.—Hippocampal activity consists chiefly of 7-3-cps rhythms, forming exceptional runs, somewhat regularized, and of rare alpha frequencies. Negative spikes from anterior hippocampus. Short beta spindles in central pair. High slow waves and sharp waves from anterosuperior temporal cortex.





Figs. 1B and 1C.—*Min* denotes effective duration of tracings here and on the other Figures, without stops in leading. Hexobarbital (Evipal) sodium given intravenously at a rate of 25 mg. per 20 seconds induces an initial increase of hippocampal spike activity (*1 min.*); however, deep sleep causes flattening of hippocampal background activity and rarefaction of spike discharges (*4 min.*); many spikes of about 500μv occur contemporaneously in the superior temporal electrode. Slow waves increased also in the central region.

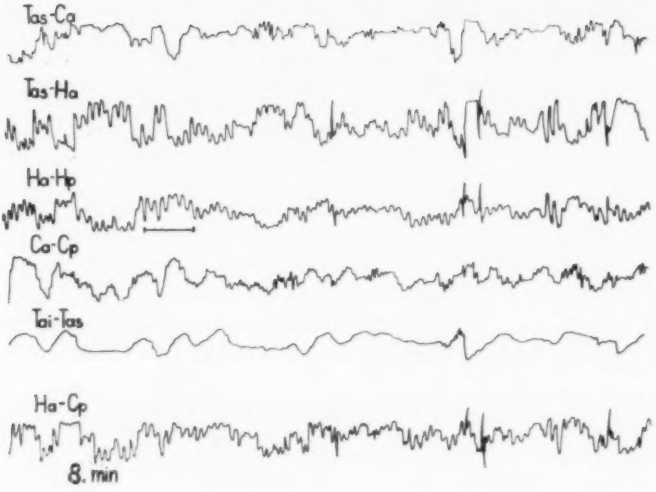


Fig. 1D.—Spontaneous lessening of sleep depth produces continuous sinusoidal 6-8-cps rhythms, coming exclusively from the anterior hippocampal electrode. Temporal spike activity decreases during this stage.

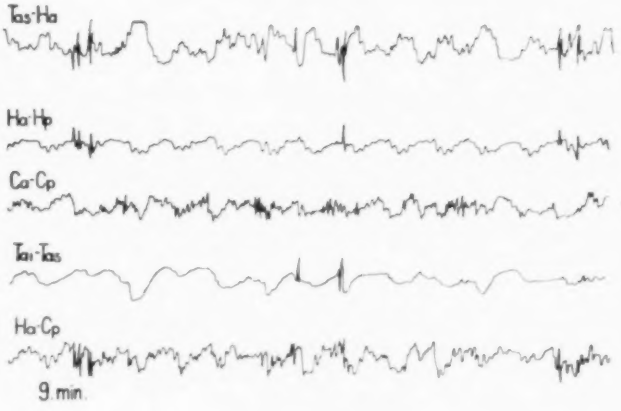


Fig. 1E.—During light sleep produced by a second gram of hexobarbital from the hippocampus, there is a scarce theta rhythm (*15 min.*); this is more conspicuous later (*17 min.*). Arrow marks start of sensory stimulation.

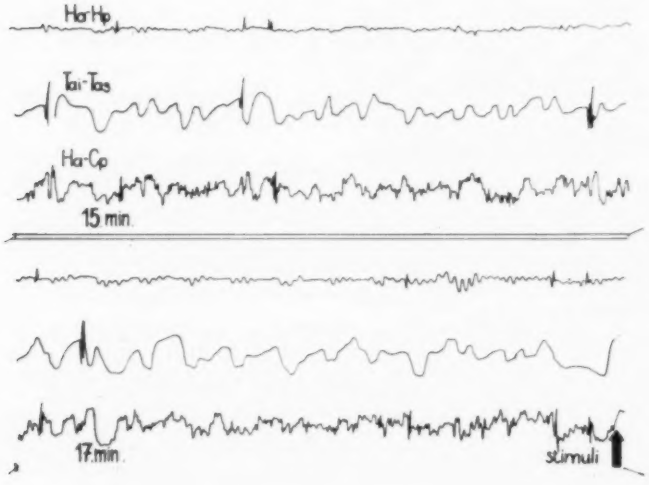


Fig. 1F.—Further lightening of anesthesia is associated with decrease of the sinusoidal rhythm, while convulsive activity of temporal cortex is reinforced.

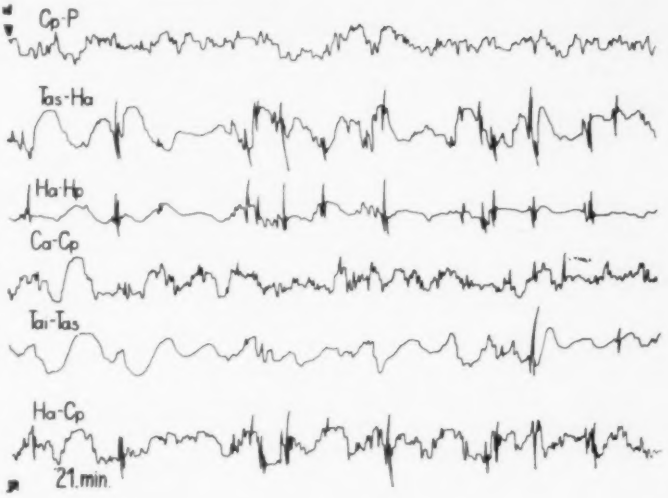


Fig. 1G.—After sensory stimulation there are only small groups with slackened regularity of sinusoidal activity from the hippocampus. Hippocampal discharges are multiplied and reach high voltage, while temporal discharges show little change.

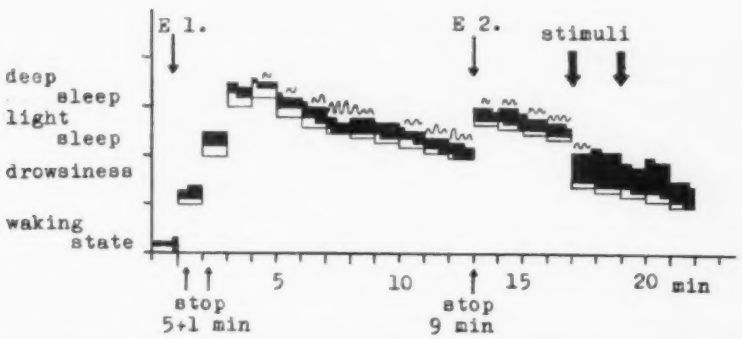


Fig. 2.—Numerical changes of the convulsive potentials produced by different levels of anesthesia and by sensory stimulation in hippocampus and temporal cortex. E=1 gm. of hexobarbital (Evipal) sodium given at a rate of 25 mg. per 20 seconds; dark rectangles indicate discharges from hippocampus; hollow rectangles, discharges from temporal neocortex: One square millimeter of the diagram equals one spike or sharp wave. Note contrasting patterns of hippocampus and temporal cortex during sleep activation. Sensory stimulation increases by fivefold the number of hippocampal discharges during drowsiness as compared with the waking state. Sinusoidal waves show degree of hippocampal synchronization, being most prominent in light sleep. Full development of synchronization is accompanied by a minimum intensity of temporal convulsive activity (eight minutes).

times, not only during the day but also at night. Seizures were initiated by loss of consciousness, followed by mastication and automatism, and occasionally by a generalized convulsion. There was total amnesia for all seizures. Drug therapy was without success.

Examination revealed moderate deterioration of psychic functions and a considerable dilatation of the right temporal horn in the air encephalogram.

EEG tracings showed a great number of spikes from the middle external temporal and the inferomedial surface on the right under hexobarbital anesthesia; deep sleep proved to be the most suitable level for analyzing spike activity. Some convulsive discharges were also seen in the left anterior temporal region when the patient was coming out of sleep.

Temporal pole resection was carried out along the anastomotic vein of Labbé on July 5, 1956 (Dr. Farago). A cortical scar of bean size was excised from the first and second temporal gyri just posterior to the anastomotic vein.

Brain tissue examined did not include the hippocampal formation because of its removal by suction.

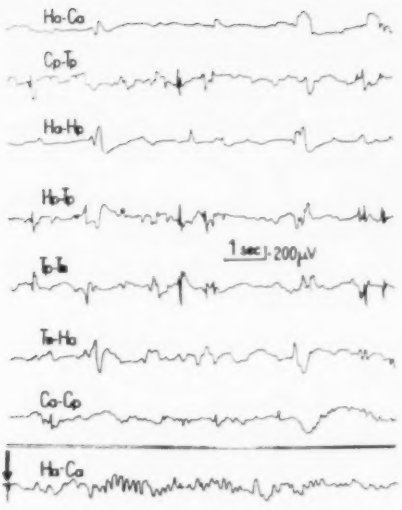


Fig. 3A.—From area adjacent to scar, chiefly positive spikes; from hippocampus, sharp and slow waves. The separate tracing at the bottom was made immediately after electrical stimulation of the hippocampus. Arrow marks stimulation.

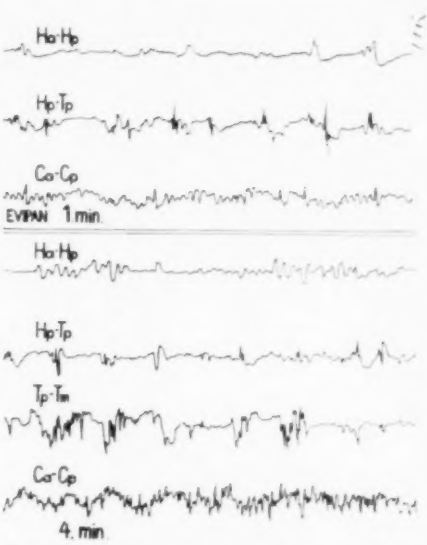


Fig. 3B.—Hexobarbital (Evipal) sodium, 25 mg. per 10-20 seconds, results in a transitory increase of temporal spike activity (*1 min.*); nevertheless, number and voltage decrease under drowsiness (*4 min.*). At that time, regularized runs of theta and delta frequencies occur from the anterior hippocampus. A relation of runs to movement artifacts in Lead *Tp-Tm* is to be recognized.

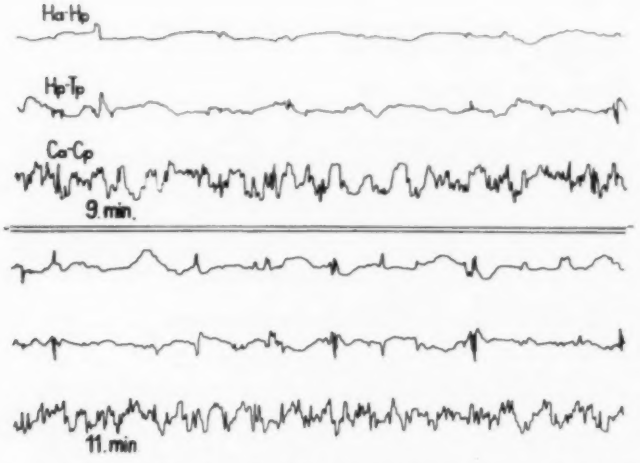


Fig. 3C.—Both hippocampus and temporal cortex show a background activity flattened during deep anesthesia (*9 min.*); convulsive discharges are reduced; when anesthesia becomes less deep, electrical activity is brisker, including convulsive activity (*11 min.*).

Figs. 3A-3E. (Case 2).—*Tp* indicates posterior temporal electrode behind the anastomotic vein of Labbé, near cortical scar. *Tm* indicates middle temporal electrode before anastomotic vein. Other labelings have the same meaning as in Figure 1.

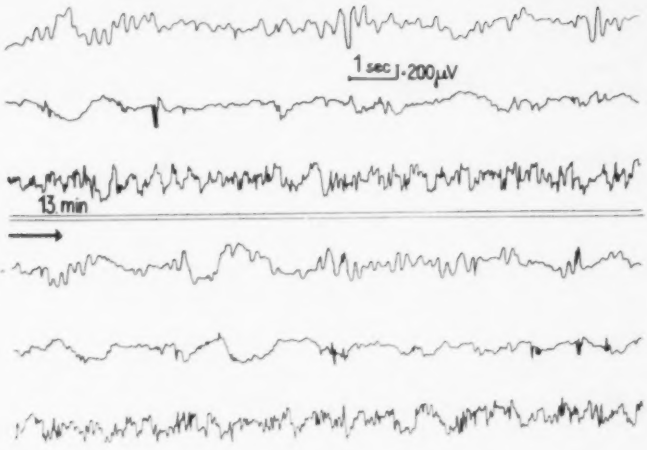


Fig. 3D.—Sinusoidal activity continuously produced by the anterior hippocampus during light sleep (*13 min.*).

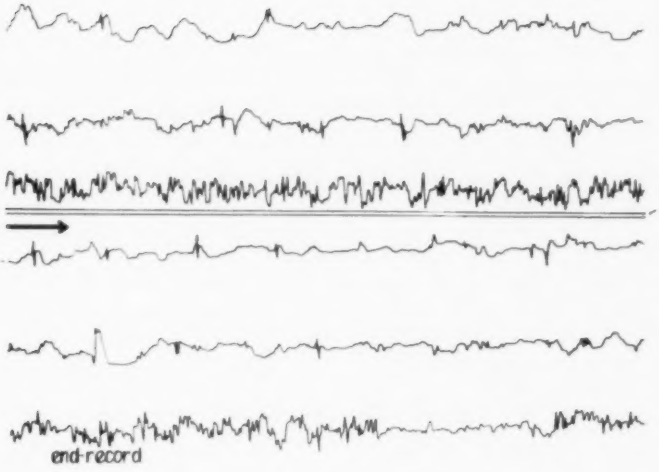


Fig. 3E.—Spike discharges of hippocampus appear most intensely in drowsiness during the last 22 seconds of observation. Negative and positive spikes and sharp waves are obtained from the hippocampus. Sinusoidal sequences have ceased. Awakening is near, as seen from sleep activity of the central electrode pair.

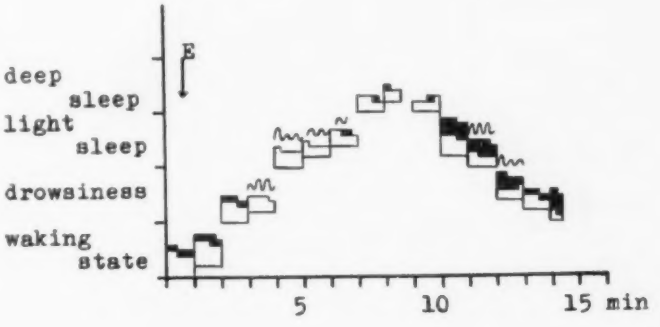
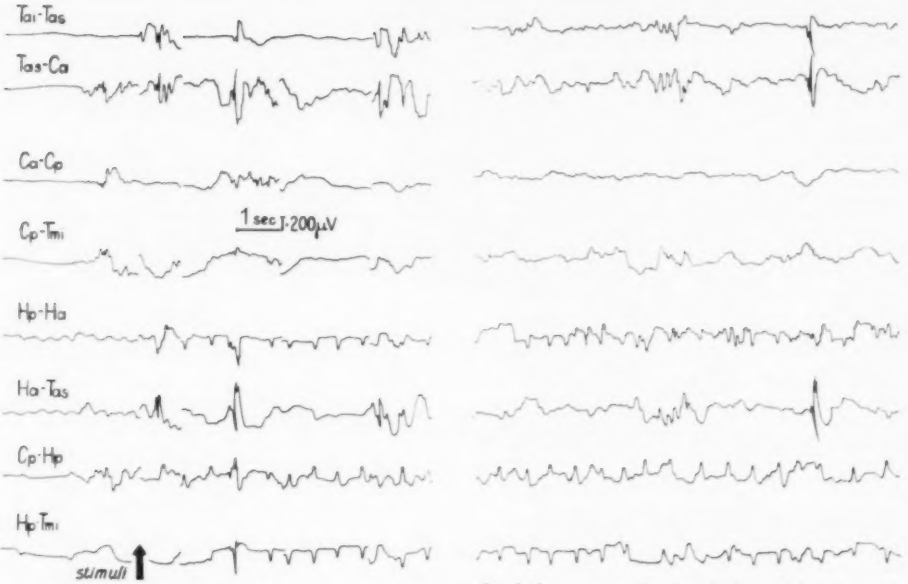


Fig. 4 (Case 2).—Hippocampal convulsive activity is diminished greatly in course of deepening of sleep and completely abolished in a certain number of minutes; on the contrary, it is increased under lightening of anesthesia, as compared with the waking state, particularly during the last 22 seconds. Sinusoidal background rhythm dominates during light sleep.



Figs. 5A and 5B (Case 3).—Strips selected from direct electrograms. One gram of hexobarbital (Evipal) sodium is followed by very deep sleep, as shown by isoelectric periods; low sinusoidal trains of 3 cps come from the anterior hippocampus at this level of sleep. Repeated sensory stimulation causes isoelectrical periods to be replaced by slow waves; spikes reappear again in the temporal cortex. Sinusoidal synchronization disappears, and groups are formed from 2-cps positive sharp waves in the hippocampus. These discharges make up an electrical seizure of more than 20 seconds' duration.

Electroencephalography under hexobarbital anesthesia two months after operation showed only a few spikes from the nasopharyngeal leads.

Case 3.—A girl of 13 years suffered a blast injury in 1945. She had had frequent nocturnal seizures, consisting of generalized convulsions during sleep since 1952 and, in addition, attacks by day for three months. The diurnal fits were initiated by a cry, "Oh! my heart," and were followed by loss of consciousness and convulsions.

Neurological findings, an air encephalogram, and serological tests were normal.

The EEG showed spike discharges from the inferomedial and polar temporal regions on the left when pentylenetetrazol U. S. P. (Metrazol) and hexobarbital activation was employed.

Resection of the temporal pole with ablation of the uncus and anterior hippocampus was carried out on Sept. 26, 1956 (Dr. Hullay).

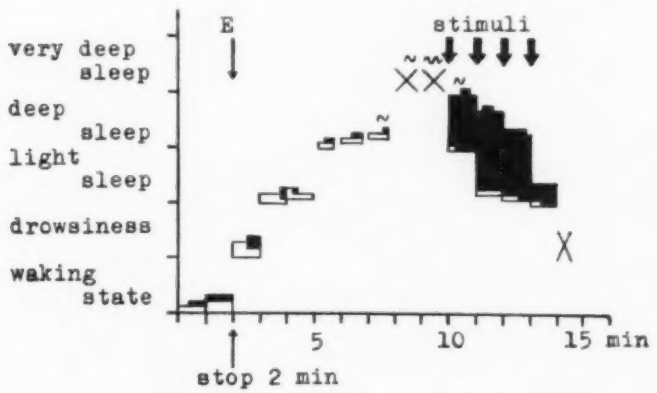


Fig. 6 (Case 3).—Convulsive activity is completely suppressed by very deep sleep, designated by *X*; however, sinusoidal waves reach their culmination at the same time. Repeated sensory stimulation induces a mass appearance of convulsive discharges in the hippocampus, mainly during light sleep, while drowsiness is free from discharge.

The removed piece of temporal lobe, including the hippocampal structures, showed no lesion.

The postoperative EEG showed no convulsive potentials even with the patient under hexobarbital anesthesia combined with acoustic and nociceptive stimulation.

Comment

Background and convulsive activities of the hippocampus of patients with temporal lobe epilepsy were recorded and studied during various stages of sleep in an interesting fashion.

The hippocampus responded to the administration of a barbiturate (hexobarbital) with a characteristic, well-regularized synchronization during certain levels of anesthesia. This synchronization seems to be similar to the electrical manifestations during spontaneous sleep of animals. During spontaneous sleep in cats, the hippocampus develops a long-lasting synchronized activity in the moderately deep phase of sleep, while desynchronization appears concomitantly in the neocortex.[25] Hippocampal synchronization does not develop while the subject is falling asleep, and it is suppressed by deep sleep. However, spontaneous awaking is accompanied, again, by long, continuous synchronization originating from the posterior hippocampus.

The sinusoidal activity of our patients differed somewhat from that of the animals. Thus, its full development occurred also in the very deep phase of sleep in man, although in a single case. In addition, sinusoidal rhythmic waves did not always derive from the posterior hippocampus, but, in contrast to the origin in animals, they came from the anterior hippocampus in the cases in which hippocampal structures were not injured surgically. Nevertheless, the hippocampal synchronization had the same morphology in man as in the animal. It was strictly confined to the hippocampus (the amygdala was not examined), and, further, it contrasted sharply with the contemporary sleep activity of the neocortex.

These facts permit us to conclude that barbiturate synchronization of the human hippocampus observed by us is produced by normal physiological mechanisms and not by an epileptic disturbance. It is equivalent to the spontaneous sleep synchronization of the animal hippocampus. Synchronized activity induced by hexobarbital anesthesia and by electrical stimulation in our cases seems to prove that the hippocampus has just as high a tendency toward synchronization in man as in animals. In animals, the special tendency of the hippocampus to respond with synchronized activity under the influence of arousal or social intercourse was first observed by Jung and Kornmüller[11] and was recently confirmed by many other authors.[1,6,17-19] However, slow rhythms of the same type could also be elicited by electrical stimulation of the mesencephalic reticular formation.[23]

The authors mentioned above pointed out a reciprocal relationship between hippocampus and neocortex in regard to the spontaneous electrical patterns in the waking state and in natural sleep. When a sequence of high rhythmic slow waves (synchronization) appeared in the hippocampus, fast low activity (desynchronization), or "arousal," developed simultaneously in the neocortex. It could be evoked by peripheral sensory stimuli, as well as by direct electrical stimulation of the reticular formation of the brain stem. These contrasting patterns of the allocortex and the isocortex were manifest particularly during the transition from drowsiness to wakefulness and under the effect of reserpine.[20]

Such an inversion between waking hippocampus and neocortex could not be demonstrated with certainty in the cases reported here. Nevertheless, a few groups of fast rhythms from central and temporal areas were associated with regularized slow-wave runs in the hippocampus during light sleep and drowsiness.

The full development of hippocampal synchronization resulted not rarely in the reduction, or even complete abolition, of the convulsive activity (Figs. 2, 4, and 6).

of the animal hippocampus. This rhythmic activity, as well as that obtained by electrical stimulation, is thought to demonstrate an inherent tendency of the human hippocampus to respond with synchronization.

Hippocampal spike discharges can be intensely activated by light sleep and drowsiness, particularly in the awakening state. Awakening produced by strong sensory stimulation is more effective than spontaneous lightening of anesthesia. A distinct inversion between activation of hippocampal discharges during sleep and that of temporal neocortical spikes may be observed during various stages of anesthesia in a case with sclerosis of the cornu ammonis.

Background slow activity, as well as spike potentials of the hippocampus, was suppressed by deep sleep in all but one case.

A primary pathological focus confined to the hippocampus may establish a secondary functional focus in the temporal neocortex, and vice versa.

University of Debrecen Medical School.

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This interesting antagonism reminds us of the suggestion that the normal and slow rhythms may have some anticonvulsive protective function.[4,12]

The striking activation of hippocampal discharges obtained by afferent stimuli is in part to be explained by the fact that stimulation initiates or pushes forward lightening of anesthesia. Figure 4 shows that spontaneous awaking raises threefold the intensity of hippocampal discharges as compared with wakefulness. However, Figures 2 and 6 demonstrate that sensory stimuli given repeatedly augment the number of convulsive potentials fivefold to fourteenfold; that is, stimulation increases the activating effect of the awaking process. Nociceptive stimuli have perhaps a particular significance for sleep activation of the hippocampus, as the hippocampus participates in emotional responses and its reactions may be amplified by affective stimuli.[25]

The fact that light sleep and drowsiness are the most favorable states for enhancing hippocampal convulsive activity is of importance in regard to the question of nocturnal fits. In addition to Case 1, we have five other cases in which histological examination showed pathoanatomical changes only in the cornu ammonis.[9] All but one of the patients stated that their seizures appeared initially at night during sleep and later on also in the daytime. Thus, one may suppose that nocturnal appearance of seizures has a close relationship to the hippocampal focus. Consequently, it may be assumed that a group of patients with primary nocturnal fits has a focus in the hippocampus. Another group, however, may have a focus in neural structures connected closely with the hippocampus by direct pathways.[3] Presumably, the positive spikes from the posterior hippocampus in Case 3 were potentials conducted from the related extrahippocampal neuron population situated subcortically.

Convulsive potentials of the hippocampus were strikingly activated by lightening of sleep, while discharges of the outer temporal cortex, rather, were activated by deepening of anesthesia. Thus, some inversion of the hexobarbital effect was noted between allocortex and isocortex. This relation is assumed to reflect functional and structural characteristics of the neuron groups activated. Careful exploration during all levels of the deepening and lightening of sleep, especially when combined with sensory stimulation, may help to discriminate between hippocampal and neocortical temporal discharges in the electroencephalogram.

A small number of discharges were merely propagated from hippocampus to temporal neocortex and vice versa. No propagation was found to frontal and central cortices, as in the animal experiments.[19] Possibly, anesthesia hindered the spread of discharges, in a manner similar to the spread-restricting effect of the barbiturate (pentobarbital [Nembutal]) anesthesia upon spikes produced by pentylene tetrazol injected in the carotid artery of the cat.[26] Nevertheless, Case 1 demonstrates that a small lesion affecting the hippocampus is able to establish a secondary (functional) focus in the temporal neocortex. Presumably this process may take its course also in the opposite direction.[14,15]

Summary

Electrocorticograms were recorded simultaneously from the hippocampal, temporal, central, frontal, and insular surfaces of six patients with temporal lobe epilepsy, both in the resting state and under the effects of various activating procedures.

In the resting state, hippocampal activity displayed mostly irregular slow waves intermingled with alpha rhythms and random negative spikes. Thyratron stimulation of the intraventricular hippocampal surface elicited rhythmic 6-cps waves.

Anesthesia induced by intravenous hexobarbital resulted in well-regularized slow activity of 7-3 cps, which presents a sharp contrast to the simultaneous neocortical tracings and a similarity to the sinusoidal synchronization during sleep and "arousal"

of the animal hippocampus. This rhythmic activity, as well as that obtained by electrical stimulation, is thought to demonstrate an inherent tendency of the human hippocampus to respond with synchronization.

Hippocampal spike discharges can be intensely activated by light sleep and drowsiness, particularly in the awakening state. Awakening produced by strong sensory stimulation is more effective than spontaneous lightening of anesthesia. A distinct inversion between activation of hippocampal discharges during sleep and that of temporal neocortical spikes may be observed during various stages of anesthesia in a case with sclerosis of the cornu ammonis.

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Intracranial Arteriovenous Aneurysms

A Follow-Up Study with Particular Attention to Their Growth

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During the past 10 years studies on the clinical examination and the treatment of intracranial arteriovenous aneurysms have been illustrated by ever-increasing series.[1,6,8,9,11,16] According to our present conception these aneurysms are congenital malformations of the vessels. However, in the majority of cases the symptoms first appear during the second and third decades of life. Symptoms in earlier life are rare. Whether this is an indication that arteriovenous aneurysms increase in size with increasing age or is the result of other factors has not been established.

Knowledge up to the present on the growth behavior of these aneurysms is based on a few isolated observations. Olivecrona and Riives[8] reported a case with a 10-year interval between arteriographic studies. The arteriovenous aneurysm was localized in the posterior part of the right frontal region and appeared to have increased in size. Shenkin et al.[14] also observed an increase in size in a case with an interval of five years between arteriographic examinations. Finally, Tönnis and Schiefer[17] reported a case with an interval of 16 years between examinations. This arteriovenous aneurysm lay immediately superior to the fissure of Sylvius and showed an increase in size despite ligation of afferent blood vessels 16 years earlier.

In order to gain further knowledge on this question, we have studied 12 patients with arteriovenous aneurysms angiographically with intervals of from 1¾ to 21 years between examinations.

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Materials and Methods

The material includes 12 patients, 9 men and 3 women, with 13 arteriovenous aneurysms; 1 patient (Case 10) had 2 aneurysms. The average age of the patients at the time of the first roentgen examination was 29 years; two were 14 years old; the rest, between 22 and 42 years of age. The site of the malformation was subfrontal in one case, in the parietal lobe in five, in the temporal lobe in one, in and adjacent to the fissure of Sylvius in three, and suprasellar in one. Finally, in one case the aneurysm was situated in the brain stem between the posterior cerebral arteries, a site which is rare. In one case the observation period was 21 years; in three it averaged 15 years, and in the rest, 3½ years.

In one patient (Case 4) a parasagittal parietal aneurysm had been partially removed. The roentgenograms from the examination before this operation are not available. In another patient (Case 8) partial removal of an aneurysm situated in and adjacent to the fissure of Sylvius was done after an observation period of two and two-thirds years. Postoperative examination showed a remnant medial to the Sylvian fissure. This residual part of the aneurysm was again inspected after one and one-fourth years. At the postoperative examination a hemorrhage was found between the brain and the osteoplastic flap, displacing the residual part of the aneurysm mediobasally. For this reason the sketches from the lateral-view roentgenograms are not directly comparable.

The details are given in the case histories. The ages given therein are those of the patients at the time of the last roentgen examination.

The angiographic technique used has been described by Lindgren[5] and Wickbom.[18] If an arteriovenous aneurysm is visualized in a particular vascular region, other vascular regions must be examined to determine whether or not the aneurysm is connected with them. Before a possible extirpation of an aneurysm its afferent and efferent vessels must be known. Because of the rapid circulation through an arteriovenous aneurysm, the injection of contrast medium must be done more quickly and the first film be exposed earlier than usual. The first injection becomes, to a certain extent, a trial injection. On the basis of observa-

tions made then, the rate of injection or the time at which exposures are to be made or both factors can be changed. If two or more injections are used, different phases can be visualized. A series of roentgenograms is obtained comparable to that produced in rapid serial angiography. Thus, the anatomic details may well be studied with the aid of both these methods. Rapid serial angiography is less time-consuming and requires less contrast medium. It is also less trying to the patient. In six cases a rapid serial changer, described by Sjögren and Fredzell,[15] was used in the periodic check-up examinations. The degree of enlargement was the same in all the examinations, thus permitting comparison of the size of the aneurysm at the different examinations. The sizes given in the case histories were measured directly on the films. It may be difficult, of course, to measure accurately the size of an arteriovenous aneurysm, with its tangle of tortuous vessels, but, since here it is a matter of comparing the size of the same aneurysm at different times, it is relatively easy to determine whether or not its size has changed.

Report of Cases

CASE 1.—A man aged 27 had subarachnoid hemorrhage without focal symptoms in 1942, at 12 years of age.

Neurologic examination in 1942 showed cranial bruit in the left temporal region.

Angiography at that time revealed an arteriovenous aneurysm measuring approximately 4.5×3.5×3.5 cm., situated subfrontally on the right side. Its posterior border extended to the level of the posterior wall of the sella turcica. The feeding arteries were branches from the anterior cerebral artery and the inferior portion of the pericallosal artery. The draining veins were a subfrontal vein and the middle cerebral vein, connected with the transverse sinus via a superficial vein.

The internal carotid artery was ligated.

Follow-Up Examination (1956).—The patient remained symptom free until July, 1956. Since that time he had had three attacks of subarachnoid hemorrhage—the last in November, 1956—without focal symptoms.

His mental and neurologic status was normal.

Angiography showed that the aneurysm had increased somewhat in size, measuring approximately 5×4×4 cm. The afferent and efferent vessels had increased to some extent in caliber. The posterior part of the aneurysm filled with contrast medium from the vertebral artery as well, via wide posterior communicating arteries. The anterior part of the aneurysm filled also through the maxillary artery via the external carotid.

CASE 2.—A woman aged 38 between 1927, when she was 10 years old, and 1941 had had eight attacks with sudden onset of headache, vomiting, stiff neck, photophobia, and a general feeling of illness, usually requiring her to remain in bed for one to two weeks. The severest attack occurred in 1935, when she was admitted to the hospital, where subarachnoid hemorrhage was diagnosed. She was hospitalized at Serafimerlasarettet in 1948, when she had become pregnant, for evaluation of the risk involved with regard to the previous subarachnoid hemorrhages.

Neurologic examination in 1948 showed nothing abnormal.

Angiography showed a wedge-shaped arteriovenous aneurysm in the parietal region on the right side. Its base extended to the surface of the brain in the interhemispheric fissure. It measured about 3.5×4×4 cm. The feeding arteries were the pericallosal from the anterior cerebral artery, a branch from the middle cerebral artery, and the posterior cerebral artery. All arterial branches were filled with contrast medium. The draining veins were veins running along the surface of the hemisphere to the superior longitudinal sinus and a vein in the interhemispheric fissure emptying via the great cerebral vein into the straight sinus (sinus rectus). Because of its site the aneurysm was considered inoperable.

Follow-Up Examination (1955).—The patient had been completely well and able to work during the interval. Her mental and neurologic status was normal.

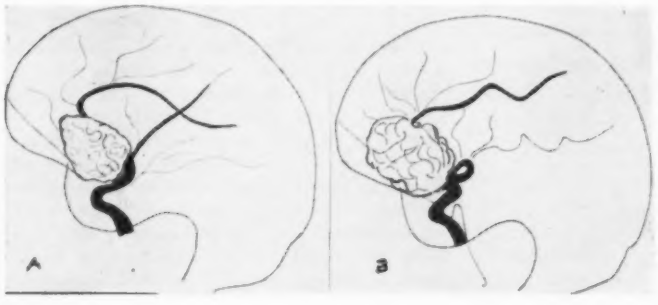


Fig. 1 (Case 1).—Angiograms: *A*, February, 1942; *B*, September, 1956.

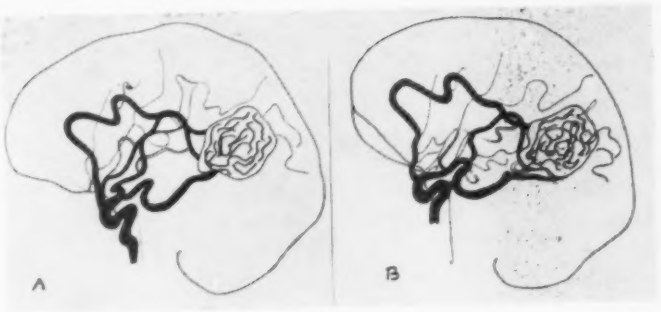


Fig. 2 (Case 2).—Angiograms: *A*, June, 1948; *B*, June, 1955.

Angiography showed, on comparison with the examination in 1948, that the size of the aneurysm was unchanged and that the caliber of the afferent and efferent vessels was the same.

CASE 3.—A woman aged 40 had a history of brief attacks of dizziness since she was 10 years old. Since she was 20 she had had mild Jacksonian fits, only occasionally associated with loss of consciousness.

Examination in 1950 showed slight underdevelopment and weakness of the left foot.

Angiography revealed a wedge-shaped arteriovenous aneurysm in the parietal region on the right side. Its base extended to the surface of the brain in the interhemispheric fissure. It measured approximately 3×5×3.5 cm. The feeding arteries were the pericallosal and callosomarginal arteries and two branches from the middle cerebral artery. All arterial branches filled with constrast medium. The draining veins were veins on the surface of the hemisphere and in the interhemispheric fissure opening into the superior longitudinal sinus.

Follow-Up Examination (1955).—There was no intellectual deterioration, but the patient was emotionally unstable.

Neurologic examination showed *status quo*. A faint murmur could now be heard in the right temporal region.

Angiography showed that the aneurysm had increased somewhat in size, measuring about 3.5×5.5×3.5 cm. The afferent and efferent vessels had not notably increased in caliber. At the time of the first investigation encephalography showed cortical atrophy.

CASE 4.—A woman aged 46 had had Jacksonian epilepsy, occurring in the form of cramps beginning in the right arm and usually associated with loss of consciousness, since she was 25 years of age. At the age of 28 hemiplegia of the right side suddenly appeared. She was admitted in 1937 to Serafimerlasarettet.

Encephalography showed a large parasagittal tumor on the left side.

Operation revealed an arteriovenous aneurysm and an intracerebral hematoma. The aneurysm was extirpated and the hematoma evacuated.

Angiography was not done preoperatively or immediately postoperatively.

The continued course of symptoms showed that the aneurysm had not been radically removed. The epileptic attacks continued. When the patient reached 33, the hemiplegia suddenly recurred on the right side, this time with aphasia. Since then she has received care at a home for chronic invalids. She was readmitted to Serafimerlasarettet in 1951, at 42 years of age, for renewed examination.

Examination in 1951 showed moderate aphasia and right-sided hemiplegia. The patient was able to walk alone. Her right arm was useless.

Angiography showed that this patient had earlier undergone operation for an arteriovenous aneurysm. A remnant was visualized, with para-

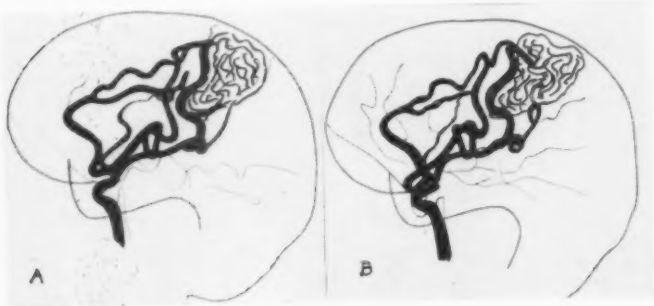


Fig. 3 (Case 3).—Angiograms: *A*, June, 1950; *B*, May, 1955.

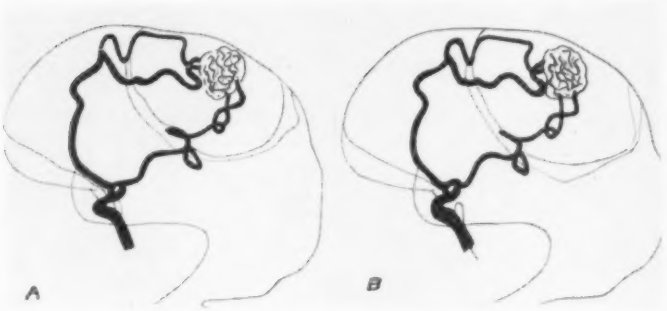


Fig. 4 (Case 4).—Angiograms: *A*, November, 1951; *B*, July, 1955.

sagittal parietal localization on the left side. It extended to the medial and superior surfaces of the hemisphere and measured approximately 3×3×3 cm. The feeding arteries were a branch from the middle cerebral artery, a branch from the anterior cerebral artery, the callosomarginal artery, and a branch from the last-mentioned vessel. The rest of the arteries in the left hemisphere were sparsely filled with contrast medium or not at all. The left carotid canal was dilated as compared with the right. The efferent veins were on the medial surface of the hemisphere and the convexity running to the superior longitudinal sinus.

Because of the patient's invalidity no measures were instituted.

Follow-Up Examination (1955).—During the previous six months the patient had become listless and apathetic, complaining of aching in the entire right side of the body.

Neurologic examination showed an unchanged condition.

The mental status showed intellectual deterioration, but the examination was difficult to carry out, owing to the patient's aphasia. She was oriented with respect to time and space and could speak, although slowly and hesitantly. She could neither read nor count and did not know here age.

Angiography showed no change in the size of the aneurysm or in the caliber of the afferent and efferent vessels. This time, also, there was sparse filling of the other vessels in the left hemisphere. The angiographic examination showed that the aneurysm took up practically all blood intended for the left hemisphere, so that scarcely any vessels were filled out in the rest of the brain substance.

Operation was undertaken in consideration of the increasing psychic symptoms. Therefore, the remaining aneurysm was extirpated with a view to improving the blood supply to possibly functioning parts of the brain.

Case 5.—A man aged 34 had, since the age of 27, had attacks of numbness in his right hand, spreading to the entire right side of the body. During the last year he had also had twitching in the arm but no loss of consciousness.

Examination in 1953 revealed no abnormality.

Angiography revealed a rounded arteriovenous aneurysm in the parietal region on the left side of the convexity. It measured about 3×3.5×3.5 cm. The feeding arteries were the pericallosal and the callosomarginal arteries and a branch from the middle cerebral artery. The anterior cerebral artery filled with contrast medium only when the carotid artery of the other side was concurrently compressed. The aneurysm was drained by an appreciably dilated vein traversing the convexity to the superior longitudinal sinus and by a less dilated vein passing over the hemisphere downward toward the pterion.

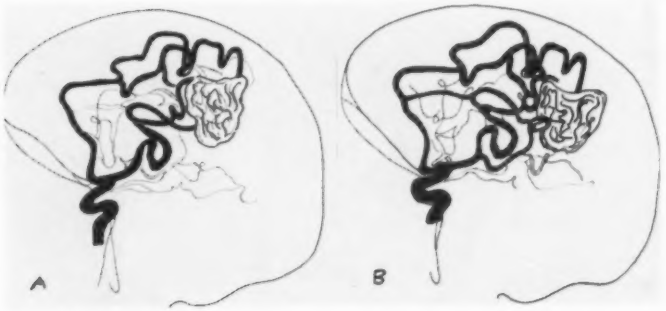


Fig. 5 (Case 5).—Angiograms: *A*, June, 1954; *B*, January, 1956.

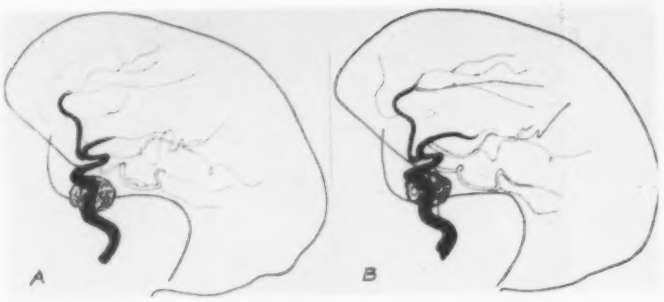


Fig. 6 (Case 6).—Angiograms: *A*, March, 1953; *B*, August, 1955.

Angiography repeated in 1954 showed no change in the aneurysm.

Follow-Up Examination (1956).—Since the previous examination fumbling of the right hand had developed. Her mental status was normal.

The angiographic follow-up after two years showed a slight increase in size to about 3.5×4×3.5 cm. and a slight increase in the caliber of the pericallosal artery and the branch of the middle cerebral artery, as well as of the efferent veins. The caliber of the carotid siphon was unchanged.

CASE 6.—A man aged 51 had a history of good health until 1937, when, at the age of 32, subarachnoid hemorrhage occurred without focal neurologic symptoms. He was subsequently well until 1940. After that time he had epileptic attacks, both brief attacks, usually beginning with photopsia in the form of "flashes and red fire" and dizziness, followed by loss of consciousness for one to two minutes, and grand mal seizures, with general convulsions and biting of the tongue, lasting about half an hour. The frequency of the attacks varied. During the last year they occurred about once a month.

On examination in 1953, the patient was mentally somewhat dull, but otherwise there was no abnormality in his psychic status.

Neurologic examination showed nothing of note.

Electroencephalography revealed abnormal activity, with the maximum in the right temporal region. Comparison with the electroencephalographic study made in 1952 showed an increase in the abnormal activity.

Angiography revealed a rounded arteriovenous aneurysm measuring about 1.5×2.5×2.5 cm. in the apex of the right temporal lobe. The feeding arteries were short branches from the posterior aspect of the middle cerebral artery; their caliber could not be determined. All branches from the right carotid artery filled with contrast medium. The efferent veins were superficial, one to the superior longitudinal sinus and one to the transverse sinus.

Follow-Up Examination (1955).—During the last year the patient had more frequent epileptic attacks. He had lost ambition and had difficulty in carrying on his work.

Examination showed no physical abnormality.

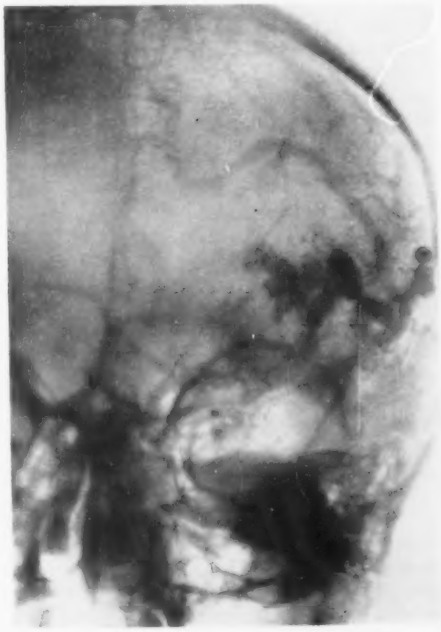
The mental status was one of probably constitutional low intelligence. In addition, there was intellectual deterioration, with extremely poor memory for both immediate and delayed recall.

Electroencephalography showed the focal abnormality to have increased in both degree and extent. It still had a maximum frontally and temporally but could be registered over large portions of the hemisphere on the right side. On the unaffected side the basic rhythm had dropped to 7 cps.

Angiography showed no change in size after two and a half years.

Encephalography showed cortical atrophy.

Fig. 7A (Case 7).—Angiogram October, 1940.



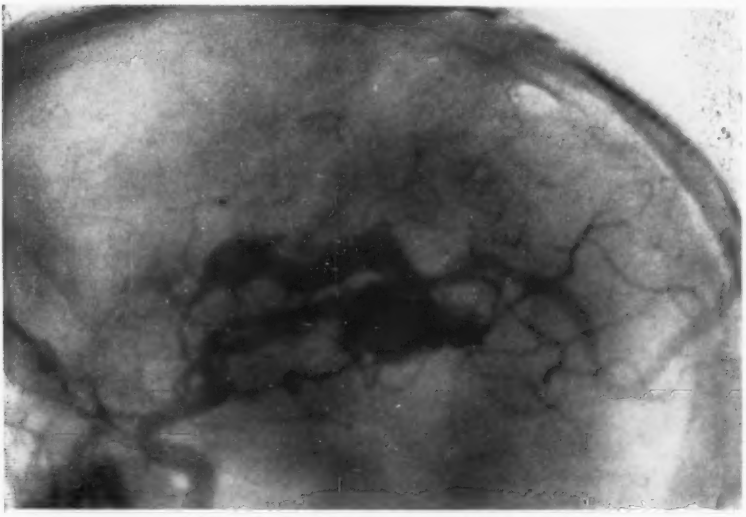


Fig. 7B (Case 7).—Angiogram October, 1940.

Case 7.—A man aged 37 suddenly sustained right-sided hemiplegia and aphasia with loss of consciousness in 1938, at the age of 20.

Examination (1940).—Powers of concentration were poor.

Neurologic examination revealed spastic hemiplegia on the right side.

Angiography disclosed a rounded arteriovenous aneurysm in the posterior part of the left fissure of Sylvius, measuring about 1.5×3×2 cm. The feeding arteries were three branches from the middle cerebral artery. All contrast medium from the left carotid artery passed over into the vessels of the Sylvian group. The efferent veins were two superficial veins running to the superior longitudinal sinus.

Follow-Up Examination (1955).—Since 1940 the weakness in the right side had decreased somewhat. The patient had had no new attacks.

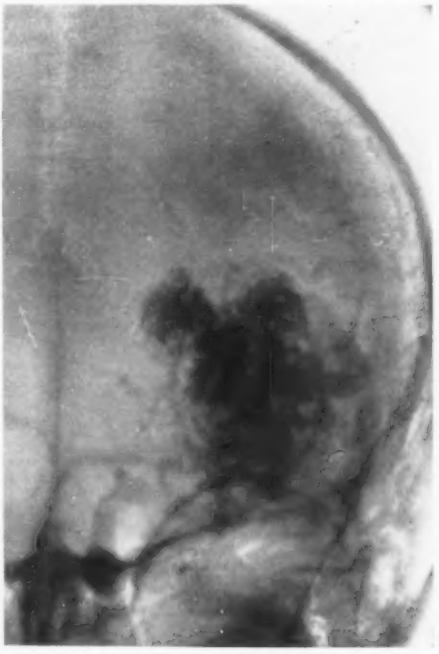
His mental status showed impaired memory for immediate recall and continued moderate aphasia with acalculia and dyslexia.

Neurologic examination showed spastic hemiplegia of the right side.

Angiography showed that the aneurysm had increased in size appreciably in the 15 years and measured approximately 4×5×5 cm. It extended farther forward and medially than before. The caliber of both afferent and efferent vessels had increased considerably; the latter vessels came from an appreciably dilated middle cerebral vein. The major portion of the contrast medium passed to the aneurysm; the rest of the Sylvian branches filled only sparsely and the anterior cerebral artery not at all. The latter, on the other hand, filled with contrast medium spontaneously from the right internal carotid artery.

Case 8.—A man aged 26 had had epileptic fits of Jacksonian type with twitching of the right corner of his mouth since the age of 20. Two years

Fig. 7C (Case 7).—Angiogram May, 1955.



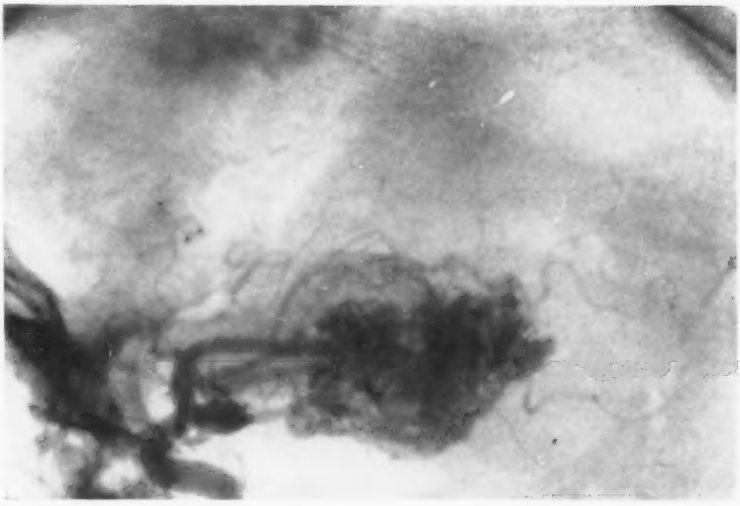


Fig. 7D (Case 7).—Angiogram May, 1955.

later a murmur developed in his head, perceived principally in the right ear.

Examination in 1945 revealed no abnormality. Cranial bruit was heard over the left temporal region.

Angiography showed an arteriovenous aneurysm in the left Sylvian fissure and its immediate vicinity, measuring about 6×5.5×5 cm. The feeding arteries were branches from the middle cerebral artery. The anterior cerebral artery did not fill with contrast medium from the left carotid. The draining veins were the middle cerebral vein and two other superficial veins, one to the superior longitudinal sinus and one to the transverse sinus.

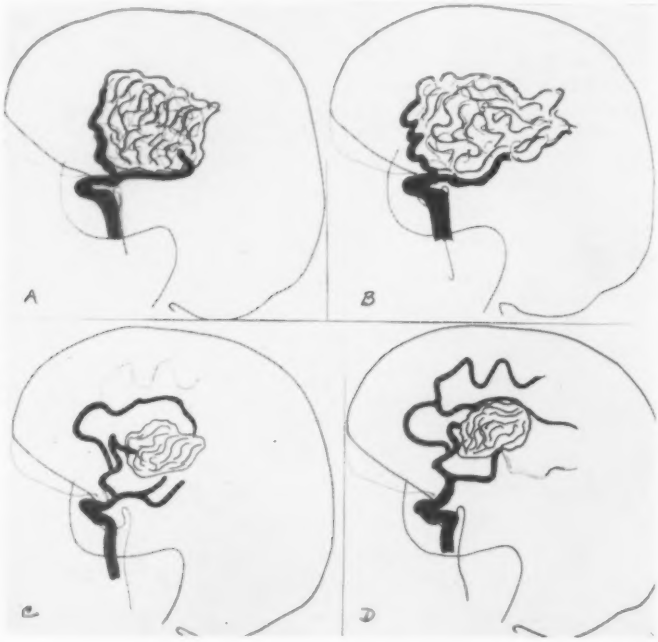


Fig. 8 (Case 8).—Angiography: *A*, February, 1945; *B*, October, 1947; *C*, November, 1947; *D*, February, 1949.

The encephalogram taken before the angiogram had demonstrated an expanding process on the left convexity at the level of the midportion of the sella turcica.

Follow-Up Examination (1947).—Somewhat increasing aphasic symptoms had been observed during the last two years.

Angiography showed that the aneurysm had increased in size, especially forward and medially, measuring about 8×6.5×7.5 cm. Numerous dilated vessels filled with contrast medium within the aneurysm. The middle cerebral artery and the feeding arteries had further increased in caliber, as had the draining veins. The anterior cerebral artery failed to fill this time also.

The aneurysm was partially removed at operation.

Angiography three weeks after the operation showed that the greater part of the aneurysm had been removed. In the most medial region there was an intracerebral remnant, measuring about 4×3.5×3.5 cm. It was fed by two branches from the middle cerebral artery. The draining veins ran along the lateral wall of the lateral ventricle to the internal cerebral vein, which was dilated. The formerly filled superficial efferent veins had decreased to ordinary caliber. The anterior cerebral artery filled with contrast medium at this time.

Angiography in 1949 showed that the residual portion of the aneurysm had not changed in size, but numerous vessels within it filled with contrast medium. Its afferent and efferent vessels had increased in caliber.

Case 9.—A man aged 43 had had Jacksonian epilepsy at the age of 24.

Examination in 1938 revealed no physical or mental abnormality.

Neurologic examination showed slight right-sided hemiparesis. A cranial bruit was heard over the left temporal region.

Angiography showed a rounded arteriovenous aneurysm in the posterior portion of the left temporal lobe and the adjacent part of the parietal lobe, measuring approximately 4×6×8 cm. The feeding arteries were branches from the middle cerebral artery. The rest of the arteries in the left hemisphere did not fill with contrast medium from the left carotid artery. Veins lying superficially over the hemisphere, running to the superior longitudinal sinus and the base of the skull, and veins to the internal cerebral vein drained the aneurysm.

Encephalography before the angiographic examination had indicated a left-sided parietal expanding lesion.

The internal carotid artery was ligated.

Follow-Up Examination (1953).—The patient stopped working in 1945 because of gradually increasing spastic hemiplegia of the right side, which temporarily confined him to bed. In association with the Jacksonian attacks, he had aphasia; sometimes he had aphasic symptoms even between attacks, especially when irritated or under stress. During the last year he had constant and extremely annoying aching in his right arm.

Examination showed no physical or mental abnormality.

Neurologic examination showed considerable spastic hemiplegia on the right and slight aphasia.

Angiography showed that the aneurysm had increased somewhat in size, measuring about 5.5×6×10 cm. The feeding arteries had become somewhat more dilated and more tortuous. The draining veins had also become more dilated. Only a centimeter-long stump of the anterior cerebral artery filled with contrast medium, the rest of the medium going to the aneurysm.

Case 10.—A man aged 35 had a history of subarachnoid hemorrhage at the age of 30, in 1950.

Clinical examination in 1950 showed nothing abnormal.

Angiography revealed a rounded arteriovenous aneurysm (10A) above the sella turcica, with its major portion to the right of the midline, but even with extension somewhat to the left also. The aneurysm measured about 2×2×2.5 cm. The feeding arteries were short branches from the middle and anterior cerebral arteries. It emptied via the greatly dilated basal vein on the right side and a vein that passed on the left side inferior to

Fig. 9 (Case 9).—Angiography: *A*, January, 1938; *B*, June, 1953.

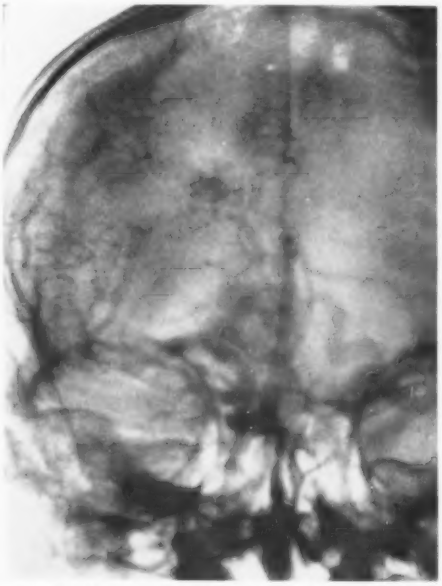


Fig. 10A (Case 10).—Angiogram September, 1950.

the brain and emptied into the sphenoparietal sinus. Other branches from the internal carotid also filled with contrast medium. In the anterior part of the caudate nucleus there was another aneurysm (10B), about the size of a hazelnut. Its feeding arteries were branches from the anterior choroid and pericallosal arteries. It emptied via the thalamostriate vein to the internal cerebral vein.

Follow-Up Examination (1955).—The patient had been well and able to work until three months before admission, when he again had a subarachnoid hemorrhage of the same type as earlier.

Clinical examination showed nothing abnormal.

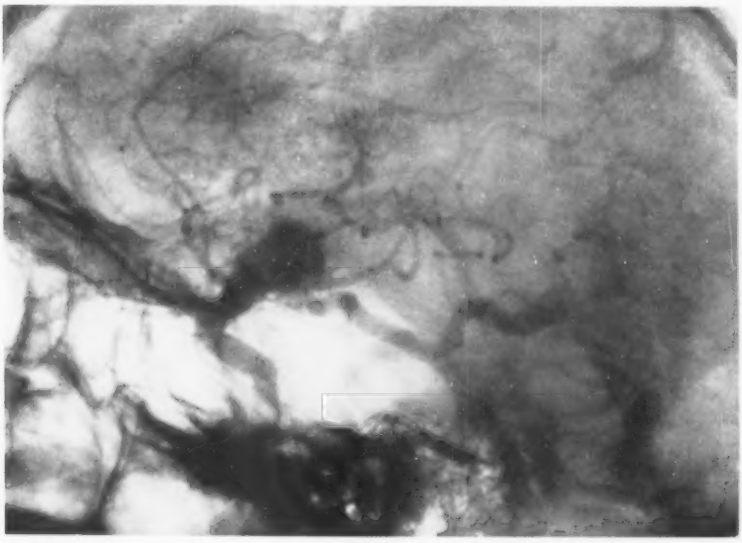
Angiography showed that the aneurysm over the sella turcica had increased appreciably in size in the interval of four and two-thirds years. It measured approximately 3×3×3.5 cm. The feeding arteries were so short that their caliber could not be determined. The carotid siphon had not changed in caliber. The draining veins had increased in caliber. On the other hand, the aneurysm in the caudate nucleus had remained the same size; its afferent and efferent vessels had not changed in caliber.

Case 11.—A youth aged 16 had had subarachnoid hemorrhage at 8 years of age, together with symptoms indicating an intracerebral hemorrhage: left-sided hemiplegia and right-sided ophthalmoplegia. His condition gradually improved. A new hemorrhage occurred in 1953. Subsequently, symptoms of considerable residual paresis persisted.

Examination in 1953 showed subnormal development of the extremities on the left side, spastic hemiplegia, and vertical-gaze paralysis upward. He was a total invalid.

Angiography showed a rounded arteriovenous aneurysm in the brain stem at the midline, measuring about 2.5×3.5×3.5 cm. The feeding arteries were both posterior cerebral arteries. Other

Fig. 10B (Case 10).—Angiogram September, 1950.



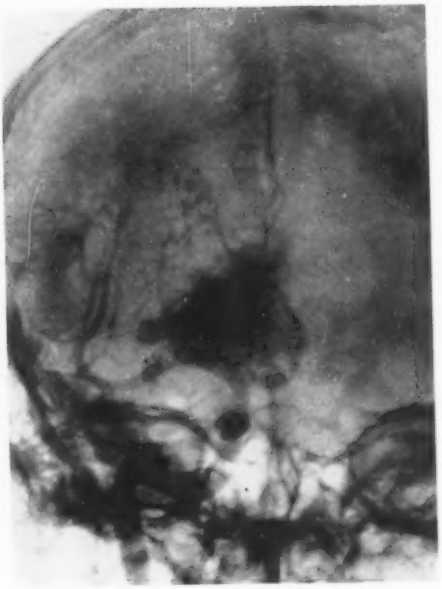


Fig. 10C (Case 10).—Angiogram May, 1955.

branches from the cerebral artery also filled with contrast medium. There were two efferent veins which emptied via the great cerebral vein into the straight sinus.

Follow-Up Examination (1955).—Psychologic examination showed a less than average intellectual level. The capacity for mechanical learning and concentration was deteriorated.

Neurologic examination showed no change.

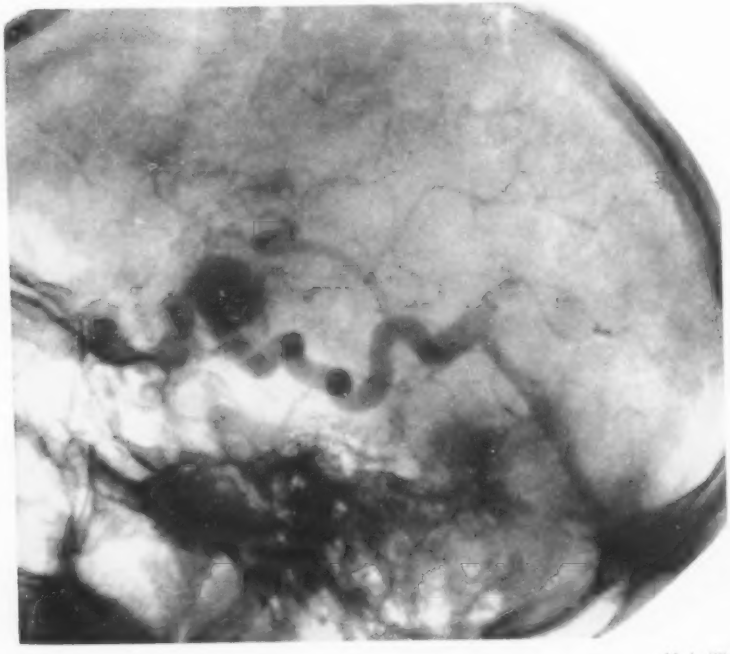
Angiography showed that the aneurysm had increased somewhat in size in the interval of one and three-fourth years, measuring about 3×3.5×3.5 cm. The caliber of feeding and draining vessels was unchanged.

Case 12.—This man was born in 1901. The early history has been reported as Case 14 in the monograph by Bergstrand, Olivecrona, and Tönnis.[1] The patient was in good health until 1931. Since that time he had had periodic severe headaches and, on some occasions, attacks of numbness in the right foot, diplopia and dizziness, noises in the left ear, and nausea and vomiting.

Encephalography in 1932 showed that the right lateral ventricle was greatly dilated and that air did not enter the left lateral ventricle.

Ventriculography in 1934 showed a considerable degree of hydrocephalus with blocking of the

Fig. 10D (Case 10).—Angiogram May, 1955.



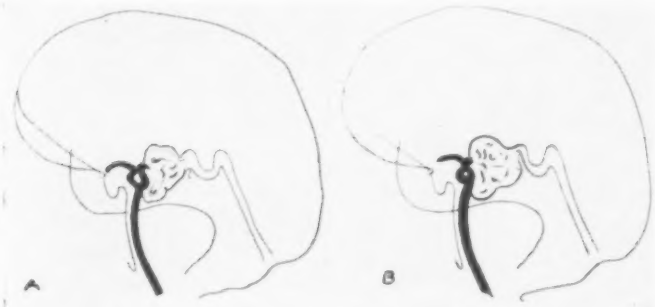


Fig. 11 (Case 11).—Angiography: *A*, September, 1953; *B*, August, 1955.

foramen of Monro. At operation, done in immediate conjunction with the ventriculography, a vascular malformation was encountered. This was interpreted as an arteriovenous aneurysm and was considered inoperable. It was observed during the operation that a dilated vein blocked the left foramen of Monro. To reestablish the interrupted communication between the left lateral ventricle and the third ventricle, an opening was made in the septum pellucidum.

Angiography in 1934 (after the operation) showed an arteriovenous aneurysm in the frontoparietal region on the left side, with feeding arteries from the callosomarginal artery and the Sylvian group. The aneurysm was emptied by several moderately dilated convexity veins to the superior longitudinal sinus and the greatly dilated thalamostriate vein, joining the equally dilated internal cerebral vein.

Follow-Up Examination (1955).—Shortly after the operation the patient was able to work and was symptom-free except for noises in his right ear.

In 1941 there was a sudden onset of hemiplegia with right facial paresis of central type. Between 1941 and 1945 he had repeated attacks of unconsciousness, lasting up to 20 minutes. He had no convulsions or similar symptoms. The right-sided hemiparesis gradually improved somewhat, and since 1950 the patient has worked as an inspector—quiet work that permits him to sit still.

Examination showed right-sided spastic hemiparesis with considerable paresis in the right arm. He gets along entirely without help, however.

Angiography showed that the arteriovenous aneurysm demonstrated earlier did not fill with contrast medium at this time. In the frontal region vascularization was sparse, consisting of both veins and arteries, but there was no sign of spasm. The vein of the septum pellucidum did not fill with contrast medium; the thalamostriate and internal cerebral veins filled little and were appreciably less dilated than formerly.

Encephalography showed the frontal region of the left lateral ventricle to be dilated to a large irregular space, which extended backward to a site immediately in front of that of the aneurysm demonstrated in 1934.

Results

Changes in Size of the Aneurysm.—In 8 of the 13 arteriovenous aneurysms an

Fig. 12 (Case 12).—Angiography, July, 1934: *A*, arterial phase; *B*, venous phase.

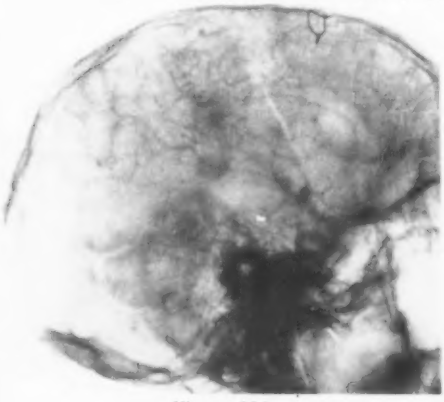


Figure 12A

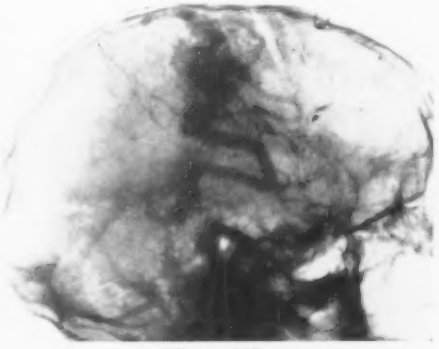


Figure 12B

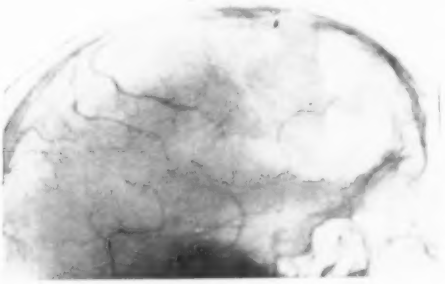


Figure 13A

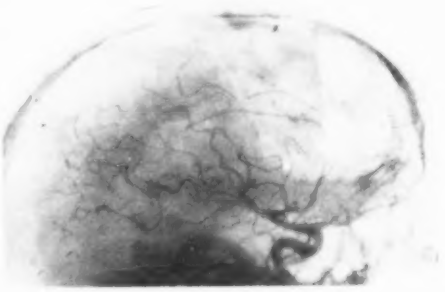


Figure 13B

Fig. 13 (Case 12).—Angiography, June, 1955: *A*, arterial phase; *B*, venous phase.

increase in size was observed at the follow-up examination. A common feature of the cases in which the greatest increase in size took place was the situation of the lesion in and adjacent to the Sylvian fissure (Cases 7, 8, and 9) and, in a fourth case (10A), in and adjacent to the cisterns above the entrance to the sella. In one case the aneurysm had disappeared.

The length of the interval between examinations varied widely. No definite correlation between the length of the interval and the increase in the size of the aneurysm was apparent in this limited material (Table).

Changes in Caliber of the Vessels.—In five of the eight cases (Cases 1, 5, 7, 8, and 9), in which there was an increase in the size of the aneurysm, there was a further increase in the caliber of the afferent and efferent vessels. In one case (10A) the arteries were so short that their caliber could not be determined; the veins showed increased caliber. In the remaining two of the eight cases (Cases 3 and 11) the increase in the size of the aneurysm was comparatively slight, and there was no increase in the caliber of the feeding and draining vessels. The same applies to the other four cases (Cases 2, 4, 6, and 10B), in which the aneurysm had not changed in size.

Case 8, in which an aneurysm in and adjacent to the fissure of Sylvius was partially removed, is of particular interest. At follow-up examination, four weeks after the operation, the superficial veins that had drained the extirpated part of the aneurysm had decreased in caliber to normal width. Thus, they had been changed in the same manner as feeding arteries when the shunt is removed. The residual part of the aneurysm drained to the in-

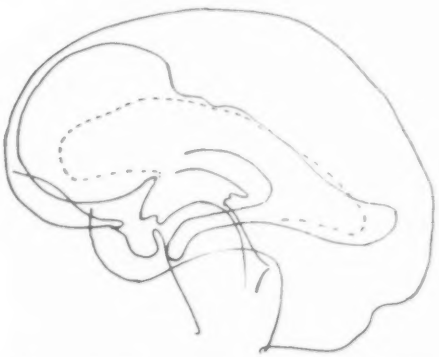


Fig. 14 (Case 12).—Pneumoencephalogram, June, 1955.

Changes in Size of Intracranial Arteriovenous Aneurysms Related to Interval Between Angiographic Examinations

Case No.	Interval, Years Between Angiograms	Increase in Size			History
		Considerable	Moderate	None	
1	14		+		
2	7			+	
3	5		+		
4	4			+	
5	2		+		
6	2			+	
7	15	+			
8	2	+			
9	15	+			
10A	5	+			
10B	5			+	
11	2		+		
12	21				Thrombosed

ternal cerebral vein, which was clearly dilated. When the follow-up examination took place, one and one-fourth years later, the residual part of the aneurysm had not changed in size, but within the aneurysm more vessels filled with contrast medium were visualized than at the previous examination. The caliber had also increased in both afferent and efferent vessels, indicating the presence of an increased shunt within the residual part of the aneurysm. Before the operation all contrast medium had passed through the middle cerebral artery and its branches. At the postoperative control examination the anterior cerebral artery and its branches filled also. This occurred at the examination one and one-fourth years later as well. Accordingly, the observations at the examination indicate that the circulatory conditions in the hemisphere continued to be more favorable than before the operation.

In Case 12 it was found at a new angiographic study, after an interval of 21 years, that the arteries filled with contrast medium to the same extent as earlier. The sparse filling of especially the veins in the frontal region corresponds to the appreciable loss of substance there. The decreased caliber of the thalamostriate and internal cerebral veins after the disappearance of the shunt through which they received the principal drainage from the aneurysm was most striking (Fig. 13).

Distribution of the Contrast Medium in the Different Vascular Regions.—In the cases presented the contrast medium was distributed within the hemisphere as follows: In four cases (Cases 5, 7, 8, and 9) only the particular vascular group to which the feeding arteries belonged was filled with contrast medium in carotid angiography. In another (Case 4) principally the feeding arteries, coming from both the anterior and the middle cerebral arteries, were filled; filling of the other arteries was very sparse. In the rest of the cases all vessels were filled in carotid angiography, as were all vessels in the vertebral region in Case 11, where the aneurysm was principally supplied from the vertebral artery.

Mental Changes and Angiographic Findings.—In two of our cases there was definite, progressive mental deterioration, notwithstanding that we found neither increased size in the aneurysm nor increased caliber in the afferent and efferent vessels (Cases 4 and 6, with intervals between angiographic examinations of, respectively, four and two and one-half years).

In one of these cases (Case 6) three electroencephalographic examinations had been performed over a period of three years. These showed a focal abnormality, increasing in both extent and severity.

Comment

Arterial Spasms.—In determining whether or not the caliber of the vessels has actually increased or decreased, one must take into consideration whether there is vasospasm. This applies to the arteries. Spasm does not appear to occur in the veins of the brain. In no case, to our knowledge, have such phenomena been described. In vasospasm the caliber of the arteries varies throughout their course, frequently so that a more or less extensive part of the artery is appreciably more constricted than adjacent parts of the same vessel. An excellent aid in evaluation is comparison with the caliber of the arteries in adjacent portions of the brain or in the other hemisphere.

Vasospasm was not observed in the cases examined.

Thrombosis.—It is well known that arterial aneurysms can become thrombosed. In certain cases extremely large sacs may be almost completely filled with thrombus, with only a small remaining cavity that fills with contrast medium at angiography. Similarly, carotid-cavernous sinus fistulas may heal spontaneously, according to Sattler,[13] in about 6% of the cases. The underlying cause, in all probability, is a thrombus. On the other hand, spontaneous thrombosis of the intracranial arteriovenous

aneurysm would seem extremely rare. Olivecrona and Riives [8] stated that thrombosis is very rarely seen in any one or several of the tortuous vessels making up the arteriovenous vascular conglomerate. Ringertz [12] reported that even in histologic analysis of these malformations he had exceedingly rarely encountered thrombi in these vessels. Norlén [7] has described an arteriovenous aneurysm in one case (Case 9) that had become thrombosed to a predominant degree as observed at operation, four months after hemorrhage. This aneurysm was very small. Paterson and McKissock [11] also reported a case in which, in connection with an occipital arteriovenous aneurysm, there was an old hemorrhagic cavity with an old, organized, laminated clot, indicating that it once formed part of the aneurysmal circulation.

In Case 12 total thrombosis of the aneurysm had taken place, resulting, among other effects, in appreciable loss of substance in the left frontal lobe (Fig. 14). A similar case has not been described previously.

Changes in Size Related to Localization of the Aneurysm.—In Case 10, in which two aneurysms were found, one, the suprasellar aneurysm, situated in and adjacent to the cistern above the entrance to the sella (Fig. 10A), had increased in size, whereas the aneurysm located in the caudate nucleus (Fig. 10B) remained unchanged in size. The greatest increase in size was observed in the three instances (Cases 7, 8, and 9), in which the aneurysm was situated in and adjacent to the Sylvian fissure. Whether or not the localization of the aneurysm influences its increase in size is difficult to decide on the basis of the relatively few cases we have been able to follow. It is possible, however, that situation in the Sylvian fissure and in and adjacent to the cistern favored the increase, in that aneurysms in these sites have greater possibilities for less restricted development than can occur when the localization of the aneurysm is mainly intracerebral. The aneurysm in the case reported by Olivecrona and Riives,[8] that by Shenkin et al.,[14] and that by Tönnis and Schiefer [17] were all three localized in or about the fissure of Sylvius.

The arteriovenous aneurysm consists of a conglomerate of intertwining, tortuous vessels with one or more afferent arteries and usually several efferent veins, which lack an intermediate capillary bed. The increase in size is probably due to gradual dilatation of these congenitally formed vessels because the vessel walls cannot resist the arterial blood pressure.

Changes in Veins After Disappearance of the Shunt.—Bunner [2] demonstrated that the dilated arteries feeding an arteriovenous aneurysm may sometimes return to normal width as quickly as within two weeks after extirpation of the aneurysm. Our Cases 8 and 12 show that even the veins can return to normal width after the shunt has disappeared.

Improvement in the Circulation Even After Partial Removal.—After total extirpation of the aneurysm the circulation may improve considerably.[2,7] Case 8 shows that even partial removal of an arteriovenous aneurysm may favorably affect the circulation in the brain because a part of the shunt is thus removed. Some aneurysms are so situated that the radical extirpation that would have been desirable cannot be done, for anatomic reasons. In these cases, if the shunt seems to be of a magnitude such that large portions of the brain receive inadequate blood supply, a partial removal could be considered. In the majority of cases, however, an operation of this type would probably present far greater technical difficulties, especially as regards hemostasis, than would total extirpation.[16]

Mental Changes.—Olivecrona and Riives [8] stated that mental changes occurred in about 50% of their cases. Lange-Cosack [4] found changes in about 70%. The symptoms usually increase with increasing age.

The mental symptoms are probably generally due to the fact that the shunt through the arteriovenous aneurysm becomes so large that the circulation through the rest of the vessels within the vascular region in question deteriorates appreciably. This is evident, among other aspects, in the examination with contrast medium, where the vessels in the vicinity of the aneurysm fill very poorly or not at all. The degree of the shunt is not directly affected by the size of the malformation but is determined by the length and width of the arteriovenous connections (Greitz[3]).

The investigation demonstrates that considerable psychic changes of progressive type may occur without necessarily being accompanied by an angiographically demonstrable increase in the size of the aneurysm or of the afferent and efferent vessels. The converse has also been demonstrated in the investigation, i. e., that an appreciable increase in the size of the aneurysm may occur without associated psychic changes. Thorough psychiatric exploration was carried out in the present series in only a few cases.

Summary

Intracranial arteriovenous aneurysms have been studied with respect to changes in size at intervals of varying length after the first examination.

The material consists of 12 patients with 13 aneurysms. The observation period was 21 years in one case, an average of 15 years in three cases, and an average of 3½ years in eight cases.

In 8 of the 13 aneurysms there was an increase in size; in the other 5 the size remained unchanged.

The increase in size was most pronounced in aneurysms situated in and adjacent to the Sylvian fissure and, in one case, adjacent to the cistern above the sella turcica.

In one case the aneurysm had become thrombosed.

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Neurological and Neurosurgical Clinics, Serafimerlasarettet.

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Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Irving C. Sherman, M.D., President
Oscar Sugar, M.D., Secretary

Regular Meeting, Dec. 18, 1956

Rabies. DR. B. H. KESERT

The history, etiology, and pathology of rabies were presented, after which a moving picture showing five cases of rabies in children was presented. These patients were hospitalized at the Cook County Hospital. The cases clearly demonstrated the clinical manifestations as seen in man, i. e., marked restlessness, salivation, spasms of the laryngeal muscles, convulsions, and finally death within two to four days. The indications and contraindications for vaccine therapy were discussed. The dangers of vaccine treatment were pointed out. Complications usually occur as the result of allergic reactions, characterized by encephalitis, myelitis, or neuritis. These complications may occur in 1 of 2000 patients treated. The ideal vaccine would be one not containing brain tissue in which the virus is grown on embryonated egg and then killed by one of various methods. To make the vaccine effective, it is important that antigens appear in the blood stream of the patient within the shortest possible time.

Discussion

DR. LEWIS J. POLLOCK: Two points should be stressed in relation to this very dramatic demonstration. First, we have here an example of the value of animal experimentation in the prevention of a disease as terrible as that which has been demonstrated by Dr. Kesert's film. If ever we have had a demonstration of the value of experimentation in the prevention of a terrible disease, we have had it in rabies. We have, in respect to antivivisection, a disease which has been made controllable by experiment.

The second point is a rather more personal account. About 1909, I was a so-called neuropathologist in the State Psychopathic Laboratories. At that time we were concerned with some experiments that dealt with, among other things, animals, particularly dogs. There was a large hound of undetermined origin in the pound that we were using for our study. At that time Dr. William H. Holmes, whom some of you may remember as a very good internist, and I were working in Kankakee. We went into the pound; this hound viciously attacked me and bit me on the thumb. Holmes, with his characteristic courage, grasped the hound in his hand, held him up, and strangled him to death with his great strength. We obtained the brain of the dog and sent it to Dr. Lagorio, who at that time was engaged in antirabic treatment. The report came back that the brain contained Negri bodies. Thereafter each day there would appear at Kankakee material obtained from the spinal cords of rabbits, which was to be glycerinated and injected into my abdominal wall. At the end of the time that my abdominal wall was subjected to these injections, it was swollen to great proportions, so that I had a large phlegmon. It so happened that, despite the fact that Lagorio had found the Negri bodies, I was a bit skeptical and obtained the brain afterward and found that the Negri bodies were actually nuclei of glial cells. I was very happy to find that the animal was not suffering from rabies, despite the fact that I had developed a great phlegmon of my abdominal wall.

There is so much disagreement remaining between those of us who are interested in the prevention of disease and those who are sentimental about animals that we can point to animal experimentation as more than justified in making human beings free of a disease that is perfectly horrible and deadly.

DR. BENJAMIN BOSHES: Dr. Kesert mentioned various animals which might be afflicted with rabies, and to that list I should add the squirrel.

During the Italian campaign, a man was brought into my ward in a very disturbed emotional state. He would cry out, tear at his hair on one side of the head, swallow a handful of hair, be quiet for a moment, and then repeat the performance. No one could get near him. Periodically he would vomit. His uniform was completely covered by recent and old vomitus.

I asked my orderly to clean the man up while I was checking over some other patients that were coming in. I returned in about 20 minutes to find the man dead. The medical orderly explained that he had offered the man some soup; the man had cried out, clutched at his throat, tore out another

handful of hair, swallowed it, suddenly started to choke, began to vomit, and suddenly died.

This caused speculation among our group. Some thought death was due to the dilatation of the stomach; others thought it was dilatation of the heart, and I thought it might even be due to a trichobezoar. At autopsy, a large bezoar was found, but not sufficient to justify the vomiting and the acute reaction. The autopsy report, some weeks later was poliocencephalitis, involving various parts of the brain; but, months later, came a report from Dr. Mallory, Fifth Army pathologist, that in the cornu ammonis numerous Negri bodies were found. This man had died of unsuspected rabies encephalitis.

In retrospect, we reconstructed the history. This man had been bitten on the side of the neck by some unknown animal, which later proved to be a squirrel. He had been given large doses of sulfonamides, and the first impression was that his illness was a sulfonamide reaction. However, the subsequent train of events indicated that the squirrel had infected the man with rabies.

The emotional reaction attendant on rabies encephalitis, with particular localization to the cornu ammonis, is referred to by Papez in his famous article on "A Proposed Mechanism of Emotion" (ARCH. NEUROL. & PSYCHIAT. 38:725-743, 1937). This area of the brain has been suspected by many as one of the pathways subserving the emotional reaction and is the basis for certain attempts at relief by local excision.

Inefficacy of Zoxazolamine (Flexin) Therapy for Spasticity Due to Spinal Cord Injuries. DRS. ALEX J. ARIEFF, S. W. PYZIK, and J. R. FINKLE.

One of the greatest problems that confronts the physician in cases of spinal cord injuries is the treatment of spasticity. Because of this, every promising drug must be tried clinically. The authors reviewed the previous literature on the clinical application of zoxazolamine (Flexin) therapy in spinal cord and cerebral disease spasticity.

In their trial therapy a total of 27 patients with spinal cord lesions having spasticity were given zoxazolamine; 3 of the patients had multiple sclerosis; 12 had quadriplegia, and 12 paraplegia, due to gunshot wound or fracture dislocations. The preliminary laboratory work was done on the urine, blood, and blood chemical components, such as nonprotein nitrogen, total protein, albumin and globulin, calcium, phosphorus, and phosphatase.

The patients were first started on 500 mg. of the drug four times a day; the following day this dose was raised to 3 tablets, or 750 mg., four times a day, and the third day the dose was raised to 4 tablets or 1 gm., four times daily. In other words, this initial trial was a rapid one, consisting of doses up to 1 gm. four times a day for a period of five to six days. Although some patients subjectively believed on one day that their spasms were better, the following day they felt they were worse. In general, there were no patients who improved on this therapy, subjectively or objectively.

Routine laboratory tests were completely normal before and after. There were no changes in the blood chemistry or in other laboratory tests mentioned.

There were many side-effects; e. g., subjectively four patients had nausea; one patient vomited; one developed edema of the eyelid. There was numbness of the leg in one patient. Nineteen patients complained of dizziness; one patient, of weakness, and four of being sleepy. One patient complained of feeling drunk, and one, of blurred vision with difficulty in focusing.

In summary, zoxazolamine, although experimentally reported to be an effective drug in spasticity, has in our clinical trials on 27 patients been of no value subjectively or objectively with respect to spasticity. In addition, it has numerous side-effects; although in larger doses it may possibly reduce spasticity, it probably does so by producing weakness, as has previously been noted in such drugs as those of the mephenesin group.

Discussion

DR. LOUIS D. BOSHES: We treated a small group of spasticity patients (six), all of whom had similar clinical pictures, with meprobamate (Miltown). Almost all the patients developed headache. One patient ran through a whole gamut of symptoms that were not present originally. The other five on meprobamate felt a great deal better eventually.

DR. S. W. PYZIK: From the reports we had, zoxazolamine had no value for spasticity. Its use for other neurologic conditions will have to be evaluated in the future.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Jan. 15, 1957

Muscular Dystrophy in the Aged: Report of a Case. Drs. Sherman E. Kapelitz and Eugene J. Chesrow.

Progressive muscular dystrophy occurring in late adult life is rare. The most recent and thorough review of cases of this type which have been reported in the literature was done by S. Nevin, of England, in 1936, who also described two of his own cases and two cases treated by his colleagues.

The case described in this report was carefully worked up, including biopsies of the gastrocnemius and deltoid muscles, in order to substantiate the diagnosis of progressive muscular dystrophy. The literature was also reviewed.

This report concerned a man aged 83 who was a patient at the Oak Forest Institutions, Oak Forest, Ill. He had been well until 11 years before admission, when, at the age of 72, he noted weakness in walking, especially in the movements of his thighs. The weakness became progressively worse, and two years later he was forced to use a cane for support. During the next two years the weakness in his thighs became gradually worse and then spread to his legs. At that time he would support himself against the table or chair in order to get about in his own home. Thereafter, the patient used a wheel chair for locomotion. Approximately two years prior to admission he began to complain of progressive weakness in his arms and shoulders.

The patient's brother, who was two years younger, had similar complaints, and they began approximately at the same time. They both consulted many physicians, but their illness was never diagnosed. The brother recently died of bronchopneumonia, before any work-up could be done.

Neurologic examination revealed marked atrophy of the deltoid, biceps, triceps, trapezius, pectoralis major, rhomboidei, supraspinatus, gluteal, and thigh muscles. However, the gastrocnemii were definitely hypertrophic. Thus, there were weakness in adduction and abduction of both upper extremities and marked weakness in flexion and extension of the forearms. There was also weakness affecting the muscles of the lower limbs, especially function of the proximal muscles, such as flexion and extension at the hip. There were no pathologic reflexes. Sensory examination was essentially normal. Cranial nerves were intact except for thinning of the facies. Bladder and bowel control were essentially normal.

Muscle biopsies revealed fragments of muscle fibers separated by adipose tissue. In some areas the muscle fibers were hypertrophied and contained several nuclei. The fat cells also varied greatly in size and shape, with infiltrations between muscle fibers. These findings are considered to be characteristic of muscular dystrophy. The clinical findings also substantiated the diagnosis.

In reviewing the literature, it appears that only 32 cases of progressive muscular dystrophy or degeneration in late adult life have been described. However, in five of these cases there was evidence of primary disease of the central or peripheral nervous system; thus muscular dystrophy was not considered. In the remaining cases there were one patient 80 years of age and 2 patients who were 70 years old or over. Nine patients were in the 60's; eight, in the 50's; six, in the 40's, and one was 32 years old. Onset in 2 of the 26 cases was in the 60's; in 7, in the 50's; in 12, in the 40's; in 3, in the 30's; in 2, in the 20's, and in 1, below the age of 20. Thirteen of the above cases had either autopsy or biopsy.

It is interesting to note that progressive muscular dystrophy can occur and have its onset clinically in the aged population. These findings may aid in the understanding of this dreaded disease.

Slides were used to demonstrate the present case, microscopic studies, and the case studies reviewed in the literature.

Inheritance of Muscular Dystrophy: A Symposium. Drs. Louis D. Boshes, H. Kravitz, A. B. Shafer, and E. E. Gordon.

Dr. Louis D. Boshes: A set of male identical twins, now 15 years of age, have been studied over a period of six years for muscular involvement. No family history of neurologic or primary muscular disorder apart from the condition in pair was obtained from an exhaustive investigation. The parents were not consanguineous.

A., the more involved twin, was slow in development and presented symptoms of increasing weakness first in 1951. Early he was ataxic, with marked weakness of the lower extremities. There was a slight lordosis but no obvious atrophy. The shoulder girdle was uninvolved. All laboratory studies were nonconfirmatory. Some eight months later the neurologic picture was about the same except for progression to the upper extremities, including atrophy of the small hand muscles. Muscle biopsy findings were interpreted as compatible with muscular dystrophy. A 24-hour speci-

men of urine contained 1025 mg. of creatinine and 375 mg. of creatine. Progression of weakness was observed in the next three years to include difficulty in swallowing solids and liquids, although there were no objective signs of bulbar weakness. Under routine supportive management for muscular dystrophy he seemed to improve, but some seven months later general muscular atrophy began to develop. Speech became thick; ataxia of the upper extremities became marked, and the gait was definitely unsteadier. On readmission for more observation and study, it was noted that respiration motion was limited, speech was more dysarthric, and there were increased signs of cerebellar deficit. The usual sensory modalities were blunted below the knees. Deep tendon reflexes were absent everywhere, and the abdominal reflexes were preserved on the left. Talipes equinovarus was seen on the left; drop foot, on the right. A repeat biopsy was again confirmatory for muscular dystrophy. Excretion of creatine was 1489 mg., and performed creatinine was 1341 mg. The laboratory profile was otherwise normal. The condition of this twin is the more progressive to the present.

B., the second of the identical twins, presented weakness somewhat later than his brother, and, although their courses have been parallel, his involvement has been, and still is, less severe. An initial biopsy, done at the same time as that on his twin, was interpreted as typical for muscular dystrophy. Weakness and wasting of all muscles, chiefly those in the lower extremities, were noted quite early. Later, atrophy of the small muscles of the hand was observed. He had pes planus. He was readmitted for study each time with his brother, and complete reviews were made of the neurologic picture, as well as the laboratory profile. Sensory changes were more profound in this patient, with abnormalities noted below the pelvic brim. Although all deep tendon reflexes had disappeared, he had retained the abdominal responses. Repeat muscle biopsies were always confirmatory for muscular dystrophy. Creatine and creatinine excretion quantities were almost those of his twin. Unlike his brother, this patient developed pulmonary, and later mental, symptoms, which cleared under symptomatic care. General management was similar for the two patients. Up to this point B. remains not quite so severely disabled as is his brother.

Electrical studies are described by Dr. Gordon.

Dr. E. E. Gordon: Rehabilitation in muscular dystrophy comprises several facets, as in other disabilities. Milhorst states that in the crippling stage of this disease 70% of the disability is due to weakness, the other 30% being determined by emotional factors, contractures, and "forgotten assets."

Several studies indicate little or no improvement in dealing with weakness. Contractures may be minimized or reduced, especially with continuous traction. Forgotten assets are readily exploited to the patient's gain by techniques of functional capacity designed to improve performance in activities of daily living. Emotional relationships between patient and family require more than casual attention.

In A., there was a reduced number of active motor units of low amplitude in the gastrocnemius, deltoid, and quadriceps electromyograms. B. showed little change from the normal. No fibrillation potentials were seen. The record is consistent with myopathy in A. I shall show nine slides to illustrate the electromyographic reactions. Before doing so, I must point out that these two boys showed what one would call normal reactions to direct current and tetanic stimulation; they did not present reactions of degeneration. They showed a normal response to electrical stimulation.

Discussion

Dr. Roland P. Mackay: Diagnosis in the case of these twins has first to do with their zygosity; that is, are they monozygotic or dizygotic? In appearance they seem to be monozygotic, and their disease probably supports that opinion. To establish monozygosity in twins is sometimes a very difficult task. If, in addition to physical appearance, one compares fingerprints and all major and minor blood groups, one may arrive at a probably error of 1 in 200,000. We do not know about the blood groups in these twins and can only assume that the boys are monozygotic.

As to the neurologic diagnosis, I have no doubt that the twins have muscular dystrophy. One is troubled by the sensory loss, which does not occur in muscular dystrophy, and so there may be something else here as well.

It is a mistake to think of genetic factors as operating in a vacuum. Perhaps Huntington's chorea and other highly familial diseases may be almost purely genetic, but in most cases both genetic and environmental factors operate. The presence or absence of environmental conditions which permit the genetic process to operate may often be completely determinative as to whether the genetic factor (genotype) can become manifest clinically (phenotype). Genetic factors probably determine chemical and enzymatic mechanisms which operate on such material as food or minerals, supplied by the environment. Most of the workers in genetics believe, I am sure, that there scarcely is such a thing as a 100% pure genetic trait.

There is an interesting and rare disease in which the victims are genetically unable to form organic thyroxin from the inorganic iodine supplied by the

environment. In an environment affording an abundance of iodine for all, there would be no cretinism except this genetic cretinism. But such genetic cretinism could be prevented by proper treatment with thyroxin. It is, of course, possible that any genetic defect, such as muscular dystrophy, might be obviated if only we knew how to supply the missing enzyme or its product. Thus, hereditary degenerative diseases are not without therapeutic hope.

Human reproduction follows the Mendelian law, but in many respects genetic studies on the human are exceedingly difficult. For this reason there is much doubt about the mechanism of most genetic diseases in the human patient. Muscular dystrophy is no exception, and there is disagreement on whether this or that type is dominant or recessive, sex-linked or autosomal. No classification of the dystrophies is quite satisfactory; but a few categories are fairly well documented, such as the pseudohypertrophic type of Duchenne. This appears to be a sex-limited recessive trait. Another which is not sex-linked, and which is probably a dominant genetic trait, is the facioscapulohumeral type of Landouzy-Dejerine. Another form is Gowers' type of muscular dystrophy, with predominantly peripheral wasting. I do not know what its genetic features are. Myotonic dystrophy, seen in these twins, is, of course, a genetic disease.

I must say a word about the case of dystrophy with late onset presented by Dr. Kaplitz. It is indeed a remarkable instance and worthy of report. A similar case came to my attention less than a year ago in a woman of 70. Her motor function had been normal up to the age of 60, when she could run and play with the children at picnics. Some six years ago, at 64, she began to have difficulty in going upstairs, and had to hold to the banisters. Her trouble steadily progressed. On examination she was found to have predominantly proximal muscular weakness. The iliopsoas and quadriceps femoris muscles were about 75% impaired; the sternocleidomastoids were so weak that she could scarcely get her head off the pillow. She could not get out of a chair without help. The gluteal muscles were also quite weak. There was some associated pseudohypertrophy in the deltoid and calf muscles. All tendon reflexes, strangely enough, were present, but the ankle jerks were definitely reduced. There were no sensory changes. Her electromyograms and chemical studies are not yet complete, but I feel sure that her disease is dystrophic, though beginning after the age of 60.

Dr. Alex J. Arieff: Dr. Mackay spoke about sensory findings. I wondered about the reflex loss, the ataxia, and the explosive speech. Although this disorder may be a muscular disease with genetic significance, it does not sound like a muscular dystrophy.

I, too, am not happy about the electrical findings. I took it for granted that the faradic and galvanic studies were sufficient to show that the disturbance was in the lower motor neuron. Sometimes when there is a battery of tests, we pick up other abnormalities. Regarding electromyography, I do not feel it is diagnostic here. I would say that a falling out of the units would be more typical for an atrophy. I suppose there may be a large amount of muscle atrophy, which would make a diagnosis difficult. I have been working on the electrical findings of progressive muscular atrophy and dystrophy. These findings are not consistent with our results. The addition of other neurologic findings makes it a little more difficult here to make a diagnosis of muscular dystrophy.

Dr. Benjamin Boshes: I have enjoyed the discussion. I wonder whether a few years from now we are going to be calling this disease muscular dystrophy. I wonder whether we are going to be interested in making histologic surveys, showing the change in muscle by scar tissue. I refer particularly to what Dr. Mackay said about the enzyme systems. At the meeting of the Advisory Board on Myasthenia Gravis, Dr. Lee Eaton, of the Mayo Clinic, reported a series of cases with profound muscular weakness which clinically were myasthenia gravis. All of these were associated with a small-cell carcinoma of the lung. The only difference between these cases and cases of myasthenia gravis was the failure to respond to a cholinergic drug.

Dr. Rose and his group at the University of California extracted the urine of patients with myasthenia gravis. In at least a small series he was able to identify a substance which had a blocking effect on the myoneural junction.

To come back to the subject of the dystrophies, I think we are going to depend more and more on what will be revealed by chemistry. This will enable us better to develop specific categories than the methods we are using at present. Certainly, the presence of fibrous tissue and fat in the muscle is not specific, because this develops in all cases if the patient lives long enough.

Dr. Sherman E. Kaplitz: In discussing the second twin, it was noted that there was a marked increase in the creatinine excretion on cyanocobalamin U. S. P. (vitamin B_{12}). Aminoacetic acid was given by Nevin, and it had been noted that there was also an increase in the creatinine excretion in his patients.

Dr. E. E. Gordon: Electromyographers can get rather intense about their findings. I feel I must disagree with comments of the previous speakers.

In view of the electromyographic findings I presented, I think we have to consider these patterns with two other factors in mind before we can decide whether they suggest a spinal atrophy

or a muscular dystrophy. First, during electromyography electrical silence was always present in relaxation; there was no fibrillation, such as one might expect in lower motor neuron disease. Second, where muscle did respond to the direct and faradic currents, the responses were normal. I agree that there would be some question favoring a spinal cord defect, had we found fibrillation potentials.

The paucity of motor unit discharge seen in the tracings finds corroboration in the biopsy findings in the gastrocnemius muscles. In these it was apparent that the amount of fibrous tissue and fat was far in excess of that of muscle fibers. Hence one would expect to see in such far-advanced cases relatively few action potentials.

DR. LOUIS D. BOSHES: In the six years we have known these children, we have noted various changes in the neurologic picture with progression. Recently we observed findings consistent with typical muscular dystrophy. There are cerebellar manifestations plus new speech features. We have no pure diagnosis for these children. I do not think we can give their disease an exact title. We think they are in this group if they are of the Erb or Gowers types, which overlap one another; but we are not certain. We are not satisfied, and shall continue to watch these children until the final story has been told.

Pernicious Anemia with Nervous System Involvement in Infancy and Childhood. DRS. H. J. GROSSMAN and L. TREVINO.

The authors reported two cases of pernicious anemia with nervous system involvement in children. Symptoms and treatment were described.

Discussion

DR. ROLAND P. MACKAY: The occurrence in this case of neurologic features not usually seen in subacute combined degeneration of the cord leads one to wonder whether the deficiency might produce unusual results in the immature nervous system. I refer especially to the intention tremor. Do the authors think that the immature nervous system may be more vulnerable, and in a different way, than that of the middle-aged patient?

DR. PAULINE COOKE: Seeing these cases made me wonder whether giving the folic acid was altogether advisable. I wonder whether the authors who have reported development of pernicious anemia upon treating what at first appeared to be sprue, could tell what percentage of patients with macrocytic anemias in childhood later develop pernicious anemia.

DR. H. J. GROSSMAN: Tremor was observed in the older child, and not in the younger one. The point brought out by Dr. Mackay about vulnerability with regard to age is well taken. The youngster, at 13, presents more diffuse involvement than is seen in the adult. The younger child presents more involvement, and the intellectual development has been much more permanently impaired. In both children one finds already evidence of impaired function of the nervous system.

The point Dr. Cooke made about folic acid is well taken. Very early in the treatment of pernicious anemia with these new agents, folic acid was used, and repeatedly it was found that, while there was amelioration of the anemic process, there was rapid progression of the neurologic complications.

News and Comment

ANNOUNCEMENTS

American Board of Psychiatry and Neurology, Inc.—The following examinations have been scheduled by the American Board of Psychiatry and Neurology, Inc.:

New York Dec. 15 and 16, 1958
New Orleans March 16 and 17, 1959

Communications may be addressed to David A. Boyd Jr., M.D., secretary-treasurer.

Books

BOOK REVIEWS

Der Hirnabszess. By Gerhard Weber. Price, 29.70 D. M. Pp. 188. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N (American zone). (American agent, Grune & Stratton, Inc., 381 4th Ave., New York 16), 1957.

The author presents a brief, comprehensive review of intracranial suppuration, including osteomyelitis of the skull, epidural and subdural empyema, intracranial venous thrombosis, purulent meningitides, and brain abscess, which comprises approximately one-third of the book. The discussion of each clinical aspect is preceded by a detailed consideration of pathogenesis. The review of the structure and dynamics of venous drainage described in the chapter on venous thromboses is one of the most detailed available. After a discussion of the etiology and pathogenesis of acute and chronic lesions, clinical symptoms are divided into those due to general infection, meningeal irritation, increased intracranial pressure, and focal brain disease. The last group is the basis for a comprehensive review of cerebral localization, this achievement being the first step in the management of brain abscess. He repeatedly emphasizes the nonlocalizing significance of impaired highest integrative functions. Special methods, including angiography, ventriculography, electroencephalography, and pyography, are analyzed, and their results in the author's series, of 56 patients, are compared. The methods of treatment, antibiotic and surgical, are carefully evaluated; and there is a detailed review of techniques, such as needling and aspiration, closed versus open drainage, marsupialization, and radical extirpation. A discussion of sequelae is followed by a terse résumé of practical aspects of diagnosis and treatment of brain abscess. What renders this work invaluable to the neurologist and neurosurgeon is the fact that a comprehensive, yet lucid, survey of all practical and theoretical aspects of a large series of cases of intracranial suppuration has been accompanied at each step of the presentation by a review of most of the significant literature. This makes the book an outstanding reference on the subject of intracranial suppuration.

THOMAS C. PARSONS, M.D.

Conditionnement et réactivité en électroencéphalographie. Supplement 6 of *Electroencephalography and Clinical Neurophysiology*. Edited by H. Fischgold and H. Gastaut, with a foreword by G. Grey-Walter and an introduction by A. Fessard. Price, 5800 fr. Pp. 476, with 207 figures. Masson & Cie, 120 Boulevard Saint-Germain, Paris 6e, 1957.

This volume contains the presentations made to the conference on the electrical activity of the brain in relation to psychological phenomena held in Marseille in 1955. This symposium included participants from Russia, Poland, India, and Japan, as well as the Western world, giving it an unusually broad outlook.

For purposes of publication, the presentations have been grouped somewhat arbitrarily into three divisions; conditioning and the EEG; behavior and the EEG, and reactivity and the EEG. The first division deals not with conditioning in the classic Pavlovian sense but with the production of a specific electroencephalographic response to an indifferent stimulus by repeatedly associating the indifferent stimulus with an unconditioned EEG response. Most commonly this consisted of combining a visual stimulus (unconditioned stimulus) with an auditory stimulus (conditioned stimulus) so that, with conditioning, sound produces a diminution in alpha activity. This conditioned response occurs in two phases; in the first, "generalized" stage the alpha rhythm is blocked by any sound, but with repeated stimulation with the same frequency tone, the stage of "differentiation," or specificity, is reached, when only a specific tone provokes alpha blockage. In addition, conditioning to a sound below the level of conscious perception can be accomplished, but it is much more transient than that produced by audible sound.

The phenomenon of external inhibition is considered, but any disturbing stimulus before a conditioned stimulus produces a generalized desynchrony, so that even were a conditioned response present it could not be observed. Extinction of the conditioned response with repetition is looked upon as a process of active inhibition. In animals in which the conditioned blocking of the alpha rhythm was provoked by auditory, visual, or somesthetic stimuli, it was reported

that a definite disturbance of alpha rhythm conditioning occured when the conditioned stimulus concerned a sensory system whose cortical representation was the seat of an epileptogenic lesion. In these animals, resection of the epileptogenic lesion improved the condition considerably.

The second division is concerned with a comparison of the EEG in normal subjects and that in certain population groups (young aviators) and in persons with psychiatric abnormalities; with the relation of EEG to certain modes of thought, social proclivities, and mental acts, and with the effects of hormones on the EEG in experimental animals. The third division deals with the psychiatric control of cortical electrical activity, the EEG responses to light and auditory stimuli, and the development of the EEG and reactivity in infancy.

Each division of the volume contains a number of papers dealing with specific aspects of the subject. A large part of the work is devoted to presentations from the laboratory of Gastaut, in Marseille, Fischgold, in Paris, and Walter, in Bristol. The book is directed toward neurologists, neurosurgeons, and psychiatrists, as well as electroencephalographers. For them it provides a wealth of information. For the more casual reader there are interesting sidelights on the EEG in the ecstasy of yoga and the detection of "supplementary pairs" and "complimentary pairs" of subjects on the basis of patterns of alpha activity.

The papers are published in French, but brief English summaries are provided at the end of most chapters. The latter do not always provide a clear indication of the contents of the papers themselves.

CHARLES E. WELLS, M.D.

Atlas of Clinical Endocrinology. By H. Lisser, M.D., and Roberto F. Escamilla, M.D. Price, $18.75. Pp. 476, with 148 plates (3 in color). The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1957.

In this atlas, of comprehensive scope, Drs. Lisser and Escamilla have brought together an impressive selection of high-quality photographs illustrating the various stages and manifestations of the endocrinopathies.

Matters relative to diagnosis and therapy are dealt with in the abbreviated text accompanying the graphic material. While the brevity of the written text adds to the value of this book as a reference source, it also occasionally leads to an unfortunate bias. Particularly with respect to therapeutic measures, the authors frequently propose measures which, while acceptable, are not necessarily preferred in all quarters.

In a field fraught with diagnostic difficulties, the authors, by stressing the pictorial aspects of the endocrinopathies, have made a significant contribution to the better recognition of the endocrine disorders. Their book should prove valuable to all engaged in the bedside practice of medicine.

J. R. BUCHANAN, M.D.

Pathogenesis and Surgical Therapy of Involuntary Movements (in Polish). By Jerzy Chorobski. Pp. 163. Panstowowy Zaklad Wydawnictw Lekarskich, Warszawa, 1957.

The author attempts to demonstrate that the involuntary movements which characterize the so-called extrapyramidal diseases are not necessarily caused by lesions of the basal ganglia. In a majority of cases the lesions are multiple, and it is not clear which one should be considered as responsible for a given symptom. He reports on a group of 12 patients with involuntary movements and brain tumors (one tumor in the occipital lobe and the others in the frontotemporoparietal region, none being in the basal ganglia). Movements ceased after resection of the brain tumor, thus supporting the idea of a functional, rather than an anatomical, cause of these movements. In each of 30 patients with a variety of involuntary movements, he sectioned the corticospinal tract or the motor cortex. In eight of these patients the movements ceased and the patients were able to return to their previous occupations. He concludes that to obtain good results following surgery for involuntary movements it is necessary to paralyze the patient at least temporarily and to hope that most of the paralysis will recede. It apparently did so in about a quarter of the patients operated upon. Such a hazard of permanent paralysis prevents this operative procedure from being a solution for the treatment of involuntary movements. However, the English summary of this monograph, written in Polish, is an interesting, straightforward, simple statement of a very complicated problem, and the author is to be congratulated.

FLETCHER MCDOWELL, M.D.

Affeciones vasculares quirúrgicas del encéfalo (Surgical Vascular Diseases of the Brain). By Alfonso Asenjo, Enrique Uiberall, and Juan Fierro. Pp. 303, with 162 Figures. Empresa Editora Zig-Zag, S. A., departamento de libroz, ave. Santa Maria 076, Santiago, Chile, 1957.

This is the second edition of the authors' monograph on "Surgical Vascular Diseases of the Brain" (written in Spanish), which was first published in 1945. It is profusely illustrated, with 162 figures. Its drawings and statistical tables are clearly presented and informative. Perhaps the outstanding contribution of this volume, especially for those who do not read Spanish, are its remarkable photographs of patients, pathological material, and microscopic sections, and its beautiful skull plates.

The authors present their experience with over 400 patients with cerebral vascular diseases, classified under four general headings: (1) congenital vascular malformations; (2) acquired lesions (aneurysms and arteriovenous lesions of syphilitic, mycotic, arteriosclerotic, and traumatic origin); (3) tumors (angiomas and angioblastomas), and (4) mixed lesions. They state, however: "Although this book has the title 'Surgical Vascular Diseases of the Brain,' we have not included all the vascular diseases that may be benefited by surgery; rather, the book is oriented mainly toward the congenital lesions and tumors. We do not include the traumatic hematomata, either extra- or subdural; the intracerebral hematomata produced by external causes acting on a normal vascular system, or thrombosis and hemorrhage of the brain."

Differential diagnostic procedures are discussed in detail, as are the operative procedures and their results made possible by hypothermia. The authors conclude that with the new procedures of controlled hypotension and hibernation, many vascular lesions may be treated surgically, and the results are often good.

A. Zuniga, M.D.
Mario Miranda, M.D.

Narkolepsie a hypersomnie s hlediska fysiologie spanku (Narcolepsy and Hyposomnia from the Aspect of the Physiology of Sleep). By Bedrich Roth. Pp. 332. Statni Zdravotnicke Nakladatselstvi, 1957.

This Czechoslovakian monograph is well organized and is a valuable contribution. It summarizes present-day views on the physiology of sleep, accepting the description of the electroencephalographic pattern of the five stages of sleep of Loomis, Harvey, and Hobart, but subdividing these authors' second stage into three parts and observing that (*a*) after a deep inspiration the sleep-activity patterns of the EEG are replaced by waking patterns and (*b*) sleep patterns may be focal in onset. The symptomatology and classification of disturbances of sleep and wakefulness are discussed. The author reports his study of 104 patients with essential narcolepsy, stressing the highly imperative nature and the short duration of narcoleptic paroxysms, the age at onset, and the course. From his own observations on patients and their EEGs, he concludes that a narcoleptic paroxysm is indistinguishable from physiological sleep.

Seventy of his one hundred four narcoleptic patients also had cataplectic paroxysms, characterized by the electroencephalographic patterns of sleep throughout the whole surface of the brain, a diminished pupillary reaction to light, loss of all cutaneous and tendon reflexes, loss of muscle tone, and total paralysis of voluntary movement, with respiratory embarrassment in two patients. Frequently the paroxysm was incomplete, affecting only part of the body, e. g., the muscles of the back or of the lower jaw. Dissociation of sleep inhibition occurred in 90 of his 104 patients. Somnambulism occurred in 5 patients; automatic behavior, in 40 patients; isolated inhibition of highest mental functions, in 35 patients; hypnogic hallucinations, in 22 patients; postsleep "drunkenness" (difficulty in becoming alert), in 14 patients; cataplexy, in 70 patients; catalepsy, in 2 patients, and sleep paralysis, in 52 patients. He includes a number of typical and atypical case histories and describes electroencephalographic findings in 97 cases. During narcoleptic and cataplectic paroxysms, during sleep, and during the interparoxysmal period he noted frequent and marked alternation of waking and sleep patterns. He infers that the basis of all the phenomena of narcolepsy is sleep inhibition i. e., inhibition through sleep. He suggests that most probably the syndrome is a manifestation of an insuffi-

ciency of the ascending reticular system. The author gives an historical review of treatment, stresses the importance of suitable occupation, recommends ephedrine or amphetamine (Benzedrin) sulfate or, where these fail, "sleep treatment," and finds trimethadione effective in 47% of his cases of cataplexy.

The book then takes up symptoms of narcolepsy secondary to manifest disease of the nervous system and analyzes the clinical picture of 51 personally studied patients. The author devotes the last portion of the book to hypersomnia, on the basis of a study of 93 patients (29 with the "organic" and 50 with the "functional" type and 14 exhibiting postsleep "drunkenness"). Forty-nine EEGs on 24 "organic" patients were classified as follows: completely normal, 2; pathological, 1, and showing alternation of waking and sleeping patterns, 44; 14 patients showed "inert" recordings. In 60 EEG recordings in 50 cases of "functional" hypersomnia, alternation of sleeping and waking patterns was found between paroxysms, and 18 patients exhibited a marked reaction to hyperventilation.

The book closes with a summary in Russian and an eleven-page summary in English. It contains 47 full-page EEG figures and 119 tables of data. There is an extensive bibliography (without titles).

DONALD J. SIMONS, M.D.

The Experimental Subject

I. The Psychiatric Evaluation and Selection of a Volunteer Population

SEYMOUR PERLIN, M.D.; WILLIAM POLLIN, M.D., and ROBERT N. BUTLER, M.D., Bethesda, Md.

Introduction

The psychiatric evaluation of "normal" volunteers is an important adjunct to the use of such subjects as "controls" for a variety of biological, pharmacological, and psychological procedures. Reports of other investigators have dealt with the volunteer subject per se,[1] as well as the methodology involved in selecting control and experimental groups in psychiatric research.[2]

This paper reports the impressions of a two-year experience in the evaluation of 83 participants, admitted (for periods of two weeks or more) to the National Institute of Mental Health. Emphasis should be placed on the fact that such evaluation is being done routinely on all experimental subjects.

In this paper, the observations made by the psychiatrist will be utilized for the purpose of indicating ways in which the characteristics of a volunteer population can be partially predetermined. The following observations will be considered in regard to developing such methods for the selection of volunteers: 1. In a youthful subgroup, the relationship of the meaning of the act of volunteering to the presence of psychopathology will be demonstrated. 2. In an aged sample, the use of social-status variables to influence the composition of the volunteer group will be illustrated. 3. The advisability of biasing a volunteer population via physiological rather than psychological or social-psychological variables will be noted.

Two general issues will also be considered: (*a*) the uniqueness of the evaluating situation; (*b*) the volunteer as a "normal control."

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Section on Psychiatry, Laboratory of Clinical Science, National Institute of Mental Health, U. S. Public Health Service, Department of Health, Education and Welfare.

Sample

Group A included 29 youthful subjects, of whom 15 were female and 14 male. The age range was 18 to 30, with a median age of 21.

Group B included 54 aged male volunteers, with an age range of 65 to 92 and a median age of 72.

Method of Volunteering

The method by which subjects volunteered varied according to the project. The following methods were predominant:

(*a*) Self-referral on the basis of public knowledge of National Institute of Mental Health research projects.

(*b*) Volunteering through an organization which by its special characteristics is motivated to cooperate with a specific National Institute of Mental Health project—for example, a Civil Service retirees' organization with a project on aging.

(*c*) Volunteering through a religious organization which has a tradition of service for projects in areas related to the concept of public welfare—for example, the various peace sect movements.

TABLE 1.—*Incidence of Psychopathological and Psychophysiological Symptoms (Present and by History) in Twenty-Nine Young Volunteer Subjects*

Anxiety symptoms	18
Phobias	3
Psychophysiological	22
Hypochrondriacal ideas	4
Compulsions	3
Obsessions	3
Depression	3
Emotional lability	2
Multiple surgery	1
Enuresis	5
Speech difficulties	2
Fire setting	1
Homosexuality	2
Projective tendencies	3
Depersonalization	1
Schizoid withdrawal	1

(*d*) Volunteering structured by the status of being a conscientious objector, in which status one of several areas of nonmilitary service *must* be selected.

1. The Youthful Group (A)

Group A[3] was made up of 15 female and 14 male subjects. The ages ranged from 18 to 30, with the median age at 21. The male component was slightly older and further advanced in education than the female one. Respective medians were as follows: Male subjects: age, 22; education, four years of college. Female subjects: age, 20; education, two years of college. Of the 24 subjects who were members of two closely related peace churches, 11 belonged to Denomination A and 13 to Denomination B. Eleven of these twenty-four subjects were conscientious objectors. Five other subjects belong to other Protestant denominations; none was a conscientious objector.

Fifteen of the twenty-nine subjects were found to have significant psychopathology.* The presence of psychopathological symptoms was tabulated (Table 1). Utilizing A. P. A. nomenclature, diagnoses were made for 11 volunteers; for 5 of them there were multiple diagnoses (Table 2).

The conscientious objectors did not decide to enter the volunteer service as such; but, rather, in conformity with their religious beliefs, they would not enter the armed forces. Once they had made this decision, they were automatically assigned by their draft boards to the appropriate volunteer service committee of their denomination. They then chose the National Institutes of Health from a list of assignments acceptable to Selective Service. Members of the peace denominations who were not conscientious objectors did not have this type of external pressure. However, both the closely knit communal sects to which they belong strongly encourage their young people to enter volunteer service. Doing so is very much part of an ongoing, active sociocultural tradition. The group who were not members of these churches had neither the external pressure of the conscientious objector group nor the cultural tradition of the peace church group underlying their entry into volunteer service. For them volunteering represented to a greater extent a personal choice.

The prevalence of psychopathology varied in these three subgroups, in direct relationship to the extent to which volunteering appeared as a personal rather than an externally pressured or externally favored act.[3] In the conscientious objector group 3 of 11 subjects had significant psychopathology (28%), for all 3 of whom diagnoses were made; among the members of the peace church group who were not conscientious objectors, 7 of 13 subjects had significant psychopathology (59%), for 4 of whom diagnoses were made; in the group who were not members of the peace sects, 5 of 5 subjects had significant psychopathology (100%), for 4 of whom a diagnosis was made. (In the youthful Group, as a

TABLE 2.—*Diagnoses in Twenty-Nine Young Volunteer Subjects*

Neurotic reactions		6
Chronic anxiety reaction	3	
Phobic reaction	2	
Obsessive-compulsive reaction	1	
Psychophysiological reactions		1
Adult situational reaction		1
Personality disorders		6
Compulsive personality	3	
Passive aggressive personality	1	
Schizoid personality	1	
Personality trait disturbance, other	1	
Sociopathic disturbances		2
Sexual deviation, homosexuality	1	
Antisocial reaction	1	
Schizophrenic reaction, chronic undifferentiated type		1

* "Significant psychopathology" is equated with the presence of symptoms, but of an order or number insufficient for the diagnosis of a syndrome.

TABLE 3—*Admission Data in Aged Volunteer Population* *

Age range	65-92
Age mean	72
Native-born	28
Foreign-born	26
Religion	
Protestant	25
Catholic	4
Jewish	25
Present marital status	
Married or remarried	34
Divorced or separated	3
Single	3
Widowed	14
Occupational level	
Professional	11
Managerial	11
Clerical	12
Skilled worker	12
Semiskilled	8
Unskilled	0
Present income	
$8000 or more	5
$4000 to $8000	13
$2000 to $4000	11
$1000 to $2000	14
Under $1000	9
No data	2
Formal education	
None	2
1-4 yr.	4
5-8 yr.	19
9-12 yr.	14
13-16 yr.	13
17+ yr.	2

* N = 54

whole, the percentage of subjects who had significant psychopathology was 52%. There was no correlation between the sex or age of the volunteer and the presence or absence of psychopathology.)

Thus, the meaning of the act of volunteering may be categorized according to the degree of internal or external pressures. (Paid versus nonpaid volunteers would represent another aspect of this same approach.) Volunteering as such clearly does not result in a homogeneous group. There are many methods by which an experimental subject may volunteer: self-referral, organizations which have special interests, such as retired civil servants, or organizations which have volunteering for public service as a tradition, selective service, etc. In general, each method of volunteering may bear a relationship to the motivation of the group secured; within each group, individual motivation may be examined. Distribution and incidence of psychopathology in a volunteer population may be an essential aspect of such research as the effect of a new drug, the influence of psychological variables in physiological measurements, or the effect of a psychological stimulus or psychotherapeutic measure. Understanding the relationship of the meaning of the act of volunteering to the presence of psychopathology in a volunteer should aid in selecting a volunteer population in a purposive manner.

2. The Aged Sample

The aged sample was made up of 54 medically screened community-resident, male subjects, aged 65 to 92, with a median age of 72. These volunteers participated in a National Institute of Mental Health multidisciplinary study of aging.[4] The study included investigation of cerebral blood flow and metabolism; cognitive, perceptual, personality, and psychomotor function, and social-psychological evaluation. These studies were done during a period of two weeks, during which time the subjects resided at the National Institute of Mental Health; in addition, follow-up evaluations of the subject and his family were carried out in the community.

Admission data on this population will be found in Table 3.

In this sample, the psychiatric technique was elaborated to the following procedure: With each subject, three two- to three-hour interviews were conducted under standard conditions. The interviews were observed through a one-way mirror by an observer-psychiatrist, and there was a systematic rotation in the roles of interviewer and observer. Recordings of verbal content were made and analyzed. Thus, simultaneous observations underlay both the independent and the consensus ratings.

TABLE 4—*Primary Diagnoses in Fifty-Four Aged Volunteer Subjects*

Psychoneurosis		14
Depressive reaction	10	
Obsessive-compulsive reaction	4	
Adjustment reaction of late life		1
Chronic brain syndrome with slight brain damage		2
Functional psychoses		3
Schizophrenic reaction	2	
Transient psychotic episodes	1	
Personality disorders		13
Psychophysiological reaction		1
Special symptom reaction		1

Nineteen of the fifty-four subjects were free from diagnosable psychopathology. Diagnoses were made for 35 volunteers (65%); for 14 of them there were multiple diagnoses. Included among the primary diagnoses were psychoneuroses, 14 cases; psychoses, 3, and chronic brain syndromes, 2 (Table 4).

Many variables may affect group composition in regard to diagnosis, symptoms, etc., and may be used to preselect accordingly among the total volunteer population. Status variables may be of such use. Let us consider one example—the relationship of marital status and retirement to depression as a possible means of predetermining a significant sample of depressed subjects among future aged volunteers.

In an initial sample of 38 psychiatrically evaluated subjects, 13 were depressed and 25 nondepressed.[5] The depressed subjects had sustained major losses, particularly recent loss of wife or enforced retirement, to a significantly greater degree than the other group. Sixty per cent of the depressed subjects were widowed and not remarried, single, separated, or divorced, as compared with 20% of the nondepressed subjects. (Nearly 50% of the depressed had been recently widowed.) Forced retirement was more important psychologically than retirement per se, and nearly 50% of the depressed subjects experienced this disruption, as compared with 14% of the other subjects.

In our own research setting, a selection of depressed aged subjects for the evaluation of a specific drug could be done most economically and efficiently by utilizing such a method. While such data concerning status, etc., may not always be available, reasonable predictions may often be made; and comparable studies of status frequently exist. This does not mean that a continuum of psychopathology may not be desirable. It does mean that the continuum or the presence or absence of subgroups can be partially preselected so as to set up the most crucial experiment with the smallest number of patients.

3. Advisability of Biasing a Volunteer Population Via Physiological Rather Than Psychological Variables

In finding controls, an initial psychiatric evaluation of large populations may be impractical, as well as introducing its own bias.

Physiological or biochemical screening of a mass population may be a more efficient initial procedure. Psychiatric screening of groups as an initial measure may be less important in terms of multidisciplinary research than, for example, finding "high" and "low" reactors on a biological continuum. In a study by Weiner et al.[6] the concentration of serum pepsinogen served as the continuum; hyper- and hyposecretors of pepsinogen were then selected for special study. With no knowledge of the pepsinogen levels or roentgenological findings, the investigators tested the hypothesis that the hypersecretor could be differentiated psychologically from the hyposecretor and that men with, or prone to, peptic ulcer could be identified. In this project, the screening technique selects out from a large population those subgroups which are most likely to be of interest for psychiatric study.†

Let us now focus on two general issues which are relevant to the groups we have considered.

(*a*) *Uniqueness of the Evaluating Situation.*—In a review of the problem of psychiatric nosology, Szasz[7] has analyzed the relevance of the social setting to the psychiatric observations which are made. A purposive element is present in each setting

† It is important to recognize that screening "high" and "low" reactors may provide data limited to the frequency distribution of a biological phenomenon and have little relevance in providing a special group for psychiatric study. The size of the population to be screened is only one of the many factors for consideration in choosing physiological or/and psychological technique for "biasing" a volunteer population.

to the detriment of an over-all system of psychiatric classification. Szasz names a few of the settings: "the mental hospital, private psychiatric practice, the child guidance clinic, the psychoanalytic training system, military service, the court of law, and jail. . . ." In one sense, each setting (e. g., jail) provides a core diagnostic group (e. g., "antisocial behavior."). Over-all nosology serves a peripheral function.

Further, each system has had its own historical development, which includes the development of the most suitable techniques of investigation.

The evaluation of the "normal control" volunteers is in itself an *experimental* situation. Such investigation is of recent origin and has not resulted in adequate conceptualizations. Psychodynamic evaluations have not received suitable recognition in the classificatory system. In research, the fact that the control situation or setting may be different for each experiment is another complication. Finally, during stress, for example, after the subject receives a psychotomimetic drug, such as lysergic acid diethylamide, the operations and nosology appropriate to "the psychiatric setting" may become relevant (and may be different from the nosology appropriate to the control situation).‡

(b) The Volunteer as a "Normal" Control.—The recent increase in investigations of volunteer populations seems to be accompanied by an increase in emphasis on the positive aspects of the psychopathology of such populations.

The availability of experimental subjects exhibiting psychopathology may indeed have advantages; a continuum may exist in terms of the presence, intensity, or acuteness of an affective state, symptom, or diagnosis. The differential action of a drug may conceivably be demonstrated in no other way. Still, the idea that such a continuum of psychopathology is "useful," as well as the concept that "no one is normal," has led, on the one hand, to an increasing use of neurotics or other "diagnostic" groups as controls and, on the other, to a disregard of the potential advantages in the use of "normal" controls.

‡ The evaluation of volunteers under the age of 20 is especially difficult. Investigators have raised the question of excluding adolescents from multidisciplinary studies because of changing physiological status and changing psychological status, i. e., so-called adolescent turmoil. Adolescent seeking out of psychological patterns which will eventually be conditioned or automatized may well be reflected in levels of physiological function which are unique to this age group.

Comment

The concept of mental health research implies the evaluation of capacities, as well as deficits and liabilities. Built into the language and experience of the psychiatrist, evaluation of psychopathology becomes a modus operandi. While a framework of reference may conceptually deal with the "process of adaptation," it is usually tested only in the sphere of psychopathology. Qualitative assessment is apt to predominate when the psychiatrist evaluates normal subjects. Quantitative aspects are traditionally linked to such terms as "symptom," "diagnosis," and "syndrome." The comparison with the "norm" is ordinarily an implicit operation; the utilization of the "normal control" makes this explicit. Such utilization creates a relatively new category of "the psychiatric situation."

The percentage of "normal controls" in a volunteer population may depend on the meaning to the volunteer of the act of volunteering. A volunteer or nonvolunteer population is not necessarily homogeneous. The idea that a continuum of psychopathology is desirable is irrelevant if this does not fit into the design of study in a small sample of subjects.

Psychiatric evaluation permits the definition of subgroups, which make for meaningful comparisons. Nevertheless, a psychiatric "profile" may be a less useful technique in defining subgroups for psychiatric study than a physiological one, especially in large populations.

Finally, a variety of social-status variables, in addition to psychological variables, may be useful in predetermining the composition of a volunteer population.

Summary

The psychiatric evaluation of 83 "normal control" volunteers is reported. The percentage of young subjects (N = 29) who showed psychopathological symptoms was 52; the percentage of aged subjects (N = 54) who had diagnosable psychopathology was 65. The relationship of the method of volunteering, motivation, and status variables to the incidence of psychopathology is utilized to indicate methods for predetermining characteristics of a volunteer population in accordance with experimental designs. The use of physiological screening to select a population for psychiatric study is noted.

The uniqueness of the evaluating situation and the volunteer as a "normal" control is discussed.

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Feasibility of Community Clinic Treatment for State Mental Hospital Patients

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The aim of this study was to evaluate the potential effectiveness of the community psychiatric clinic as an alternative disposition for certain mental hospital admissions. Specifically, it would compare the effectiveness and costs of hospital and clinic treatment in comparable psychiatric cases. From a sample of state mental hospital admissions, patients judged suitable for outpatient treatment in community clinics would be identified; of this group, half would be released and referred to outpatient clinics for treatment, while the other half would follow the ordinary course of hospitalization. Differential consequences of these treatment dispositions would then be evaluated.

In previous studies,[1,2] conclusions had been drawn from the attempt to predict what the fate of patients would have been had they not received a particular service. The present study proposed a systematic test of these alternative dispositions.

The research design assumed that a sizable number of hospital admissions are suitable for either inpatient or outpatient treatment. A pilot study was set up to test this assumption and posed the following questions: 1. Can a sizable group of hospital admissions be treated either as hospital inpatients or as clinic outpatients? 2. Can these patients be readily identified shortly after admission? 3. Can they be easily referred from hospital to clinic? 4. What important factors characterize them?

This paper reports the results of the pilot study.

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This paper is a short report of "A Study of Suitability for Outpatient Clinic Treatment of State Mental Hospital Admissions," Research Report No. 1, 1957, published by the California Department of Mental Hygiene, Sacramento, Calif.

The study was supported by the California Department of Mental Hygiene and a grant from the National Institute of Mental Health. The original proposal was developed by Portia Bell Hume, M.D., Deputy Director of Community Services, and Richard D. Morgan, Statistical Research Officer, the California Department of Mental Hygiene.

The Setting

Three California state mental hospitals and two state community clinics participated in the project. The three hospitals are within 75 miles of the San Francisco Bay Area, where the two clinics are located. Therefore only hospital patients residing in the five Bay Area counties were selected for the main sample, for convenient referral to one or the other clinic.

Methods

The following procedures were used to select the sample of patients and to screen them for clinic suitability.

1. Every even-numbered admission to the three hospitals from the five counties for a three-month period was sampled. Patients transferred from other hospitals and those admitted only for observation did not qualify as new admissions and were excluded. Data obtained for the sample included evaluations of suitability for outpatient treatment, ratings on the patient's psychiatric condition and prognosis, copies of the mental examination and social history, when available, and, for part of the sample, an MMPI profile. Partial data were obtained on admissions from other counties for some points of comparison.

2. Potentially suitable patients were identified by the admission ward psychiatrists at two hospitals and by the examining physicians at the third hospital. The physician recorded on a special form the presence or absence of obvious contraindications to immediate referral for clinic evaluation. He was asked to judge whether the patient required continuing care in a hospital setting, not

whether he was suitable for clinic treatment. It was important to the aims of the study that clinic referral be initiated as soon after admission as possible. Therefore, only patients rated at this first screen (Gate I) within seven days after admission were defined as "new admissions" and included in the sample.

3. Patients who passed the first screen were then considered for referral to the clinic by a hospital psychiatrist and social worker. At this second screen (Gate II) patients were eliminated if they or their relatives refused to cooperate in the referral plan, if they had relapsed, or if further information contraindicated referral.

4. Referred patients were released from the hospital on a one-day or overnight pass. The patient, usually with a responsible relative, was interviewed by the clinic intake team, consisting of a psychiatrist and a social worker. At a later conference (Gate III) the clinic staff decided whether or not to attempt outpatient treatment. Patients accepted by the clinics and assigned to treatment were immediately released by the hospital on indefinite leave.

Results

Composition of Sample.—During the sampling period, there were 553 even-numbered admissions to the three state hospitals. From the sample 49 patients were excluded because they either were screened late or, by an oversight, were not screened at all. These missed cases were not excluded for any known systematic reason. The final sample, of 504 cases, thus included over 90% of all eligible patients. Over two-thirds of the 504 sample patients were actually screened at Gate I by the second day after admission.

Selected characteristics of the sample are given in the accompanying Table, as a basis for comparison with other hospital admission populations.

Screening Results.—The main finding of the pilot study is that only 6 of the 504 patients in the sample were accepted for outpatient clinic treatment. Of these 504 patients, 57, or 11%, were identified at Gate I as potential candidates for clinic referral; 20 of the 57 were referred to the clinics, and only 6 of the 20 were accepted by the clinics for treatment. The six accepted patients constitute only about 1% of the total sample.

*Selected Characteristics of the Sample**

	Per Cent of Sample		Per Cent of Sample
Sex		Occupational status	
Male	53	White collar	18
Female	47	Blue collar	42
		No occupation	31
		Unclassified	9
Age			
Under 20	2		
20–40	53	Diagnosis	
40–60	40	Alcoholic disorder	27
Over 60	25	Psychotic disorder	39
Median age = 47 yr.		Brain syndrome (other than alcoholic)	22
Marital status		Personality disorder (other than alcoholic)	7
Single	25	Psychoneurotic disorder	4
Married	55	Other	1
Divorced	17		
Widowed	14		
Separated	9		
		Legal classification	
Race		Committed as mentally ill	56
White	89	Committed as alcoholic	25
Nonwhite	11	Voluntary admission	13
		Other	6
Religion			
Protestant	55	Previous hospitalization	
Catholic	39	One	20
Other	6	Two or more	16
		No history	64
Education			
College (2 yr.+)	11		
High school (2 yr.+)	45		
Grade school (5th grade+)	43	Outpatient clinic contacts	
Less than 5 grades	1	With previous contact	8
Unknown	0	Treated 6	
		No record of treatment 2	
		With no previous contact	83
		Unknown	9

* Number of patients 504.

Although the research design required random assignment to clinic treatment of only half the accepted cases, early experience indicated that few patients would be accepted by the clinics. Therefore, in order to obtain maximum information about treatment possibilities, all six accepted patients were assigned to clinic treatment. As explained later, only four of the six actually received treatment, and only two were judged to have benefited from treatment.

Furthermore, four of the six patients, including one judged to have improved with treatment, did not meet the stipulations regarding the time limit for screening new admissions and availability for random assignment to either disposition. One patient was accepted on condition that she receive further hospital care for two weeks. Two patients who did not qualify as new admissions were inadvertently included in the sample. A fourth patient, a voluntary admission, was not subject to random assign-

ment, as she had asked for discharge and would have been released at once regardless of the clinic decision.

Only two of the original sample of patients met the exact conditions of the research design and were accepted for clinic treatment.

Reasons Given for Exclusion—Physicians at Gate 1 excluded 447, or about 90%, of the original sample of 504 patients from further consideration because they saw need for continuing hospitalization. Typically they gave such reasons as these: The patient's severe regression (confusion, disorientation) and inability to take care of himself necessitate a protective environment; physical rehabilitation in a controlled environment is necessary; special somatic therapies should be provided in an environment which permits careful supervision; the patient is a suicidal or homicidal risk; the patient should be separated from a disturbing environmental situation.

Of the 57 patients who passed Gate 1, the hospital referral teams eliminated 37 from further consideration. In 16 of the 37 excluded cases, alcoholism was either the diagnosis or a prominent symptom. The reasons given for nonreferral overlap with those at Gate 1; but the patient's unwillingness or lack of interest in outpatient treatment, or family reluctance was also emphasized.

Of the 20 patients referred to the clinics for evaluation, only 6 were accepted for treatment, 3 by each of the participating clinics. The other 14 patients were considered unsuitable for treatment. In 5 of the 14 cases so rejected, the primary reasons cited were the patient's lack of interest in treatment or the unlikelihood of his benefiting from it. It is interesting that in the nine other cases the clinic staff considered further hospitalization the treatment of choice because of the patient's need for special therapies, best provided in a supervised environment, because of suicidal risk, or because of doubts at the time about his ability to live in the community.

The screening process will be evaluated and interpreted in a later section.

Six Accepted Cases—The six patients accepted for clinic treatment were four men and two women; four of the six were in their 30's; one was 21 and the other 49. Four patients were diagnosed as schizophrenic and two as alcoholic. Three were voluntary admissions; two were alcoholic commitments, and one was a mentally ill commitment.

Among their reasons for acceptance, the clinic emphasized in five of the six cases some motivation for treatment, such as the patient's seeking help or recognizing his need for help. The capacity to use such outside help as Alcoholics Anonymous, a previous history of fairly adequate occupational adjustment, and traits such as intelligence or tolerance for frustration were listed as encouraging features.

The clinic teams, however, did not consider this group of patients promising, for on a four-point scale of clinic prognosis they rated no patient as excellent, only one as good, four as fair, and one as poor. The general impression in each case was that, though treatment could be tried, the outlook was guarded.

Treatment Outcome—Of the six patients accepted for clinic treatment, one, a woman, was returned to the hospital after a single treatment hour. Her agitation had increased as the time of hospital release approached, and family arrangements to set her up in a separate apartment had failed. With her consent she was returned to the hospital, where she remained for four months, and was again hospitalized after a month at home.

A second patient dropped out of treatment after three or four interviews. Six months after his release he was hospitalized for 11 days; a month later he returned for a more prolonged hospitalization. A third patient failed to come to any treatment hours, and contact with him was lost. A fourth patient, with a total of nine treatment interviews, skipped many appointments and arrived

drunk for others; when he dropped out of treatment he was judged to be unimproved. He was returned to the hospital seven months after his release. A fifth patient, a 49-year-old male alcoholic, after nine treatment interviews in a two-month period, was reported to show symptomatic improvement and ended treatment with the therapist's consent. The sixth patient, a 36-year-old woman with a diagnosis of psychotic depressive reaction, was still in treatment at the time of this report and was said to be making progress.

In summary, only two of the six accepted patients kept regular appointments and were considered by their therapists to show improvement.

Comment

The Screen.—The first issue in an evaluation of results concerns the screening procedures; that is, the bases for the conclusion that few patients in the sample, shortly after admission, were suitable for clinic treatment. Did the hospitals fail to refer many patients who would have been accepted for treatment by the clinics? Did the clinics reject many patients who could have been successfully treated?

No patients excluded at the hospitals were actually evaluated by the clinic intake teams, nor were patients judged unsuitable by the clinics actually offered treatment. The evidence concerning the adequacy of screening judgments is therefore indirect and limited, but consistent enough to permit some grounds for an informed opinion.

1. The data indicate that the hospital screen was in general not overconservative. Hospital screeners reported that they were following the instructions to refer all doubtful cases to the clinics for evaluation. The fact that only 6 of the 20 referred cases were accepted by the clinics indicates no overselection in the referred group, which included schizophrenics, suicidal risks, and alcoholics, as well as those with the diagnosis of psychoneurotic reaction. Evidently the hospital screeners did not operate on certain blanket stereotypes, such as "clinics don't treat psychotics" or "clinics don't accept suicidal risks."

2. Although a majority of state hospital physicians have had no experience in outpatient psychiatric clinics, about 80% of the sample of 504 cases were screened at Gate 1 by physicians with such experience. Raters with formal training in psychiatry and with experience in outpatient clinics identified a significantly smaller proportion of patients as potentially suitable for clinic treatment than did raters without such training and experience. This finding suggests that the hospital-screening results cannot be attributed to the raters' unfamiliarity with clinic criteria of suitability.

3. The data indicate that the clinics did not apply an overly restrictive standard of selection, in terms of their capacity to provide useful services for these patients. The treatment vicissitudes of the six accepted cases illustrate this point. One patient required immediate rehospitalization; a second failed to keep any clinic appointments after the intake interview; two others dropped out of clinic treatment after brief and irregular contact and were subsequently rehospitalized, and only two patients kept regular appointments and were considered to benefit from treatment. Of the two, one terminated treatment at his request after what his therapist considered a superficial involvement in psychotherapy.

We must conclude that the six accepted cases were not overselected, but, rather, that the guarded prognosis for these patients was correctly estimated. We may also conclude from the failure of three patients to maintain clinic contact that the clinic screeners did not set too high a standard of treatment motivation for acceptance.

It is true, however, that the clinics, in keeping with their practice, rejected a few cases in which a substantial amount of field social work might have succeeded in restoring the patient to the community and making outpatient care possible. They also rejected one or two patients who might have been treated if experienced staff had been avail-

able with time for daily appointments if necessary. According to the research plan, the clinics would offer ordinary levels of treatment, but would waive the waiting list, for these patients.

Community Screening.—The five Bay Area counties from which the main sample was drawn are richly staffed with private and public psychiatric facilities. Patients from these counties had therefore had earlier access to outpatient help if they were disposed to seek it and able to use it. In addition, many of these patients before their commitment to the state hospital had been briefly hospitalized in county hospitals, which offer limited treatment and also to some extent screen patients for courses other than state hospital commitment. Our sample had thus already undergone considerable screening in the community.

This may explain in part why so few patients in the sample were found to be suitable for clinic treatment. It is possible that such patients in the Bay Area are routed by various means to outpatient resources and do not enter the state hospital. The admission population from these counties may thus constitute a residual group of cases unsuitable for clinic treatment. Areas in the state (or nation) which contain fewer community screens and outpatient facilities may generate an admission population which includes more clinic-suitable cases. We do not consider our data sufficient for an informed guess about this matter. Our experience in the study, however, provides other explanations for our findings.

Time of Screening.—Patients in the sample were considered for clinic treatment while they were in the hospital, and at a point shortly after the events which had precipitated their hospitalization. These factors influenced the results in several important ways.

The restoration of the hospitalized patient to a community setting often involves services other than formal treatment. Acceptance of some patients would have required the clinics to offer, in addition to outpatient psychotherapy, some services typically provided by social agencies.

In other instances the clinics rejected, on the basis of poor prognosis, patients whom they hesitated to remove from the hospital. Before the hospital admission, there would have been less to lose in attempting treatment: Hospitalization might be averted, or, if not, relationship of the clinic with the patient and family could ease referral to the hospital.

Important in the restoration of the patient to the community are factors other than treatment agencies. From the standpoint also of the patient and his family, the period shortly after admission has become an unfavorable one for attempting clinic treatment. In the period preceding hospitalization, often one of uncertainty and conflict,[3,4] the hospital may not be a clear-cut choice; and the patient and his family may be accessible to alternatives no longer welcome after a painful resolution of their conflict by the decision for hospitalization.

Hospital and Clinic Discontinuities.—In these ways, the effects of community screens on hospital admission populations, the time at which evaluation was made, and the situation of the patient and family at that time, all contributed to the results of the study. For a majority of the sample patients, however, the results must be explained in terms of yet another issue.

The raters perceived the indications for hospital and clinic treatment as disparate, and these disparities cluster around two dimensions: the patient's need for a protected environment, and his awareness of illness and active interest in obtaining psychiatric help. At the same time, the raters did not consider hospital or clinic treatment the only choices in all cases. Some patients were seen as able to function outside a hospital, but as inaccessible to outpatient psychotherapy as offered by the clinics.

The need for a protected environment or the capacity to function outside a hospital is relative to the community supports available to the patient. In a choice between

continued hospitalization or referral to an outpatient clinic, a patient may be seen as requiring the protected hospital environment; but the same patient might be able to function in a halfway house, a foster home, or even in his ordinary social milieu, if given sufficient practical help, as by a social agency. The community clinic, which ordinarily provides little or no supervision, did not accept, during the course of this study, patients who would require considerable help in seeking employment or in finding a place to live.

Different institutions require different levels and kinds of motivation in the patient. Outpatient psychotherapy in a clinic demands from the patient some readiness to attempt the treatment and sufficient initiative or responsibility to stay with it during a trial period. Admission to a mental hospital, on the other hand, does not necessitate any motivation for treatment or change, or even require him to define his difficulties as psychiatric in nature.

Few patients in the sample were deemed simultaneously suitable for hospital and clinic care, largely because of the marked discontinuities in the amount of care the two institutions provide for patients and in the motivation they require for participation in their respective services.

Implications for Research.—The present results contrast with some prevailing opinions about the possibilities of using clinic treatment as an alternative disposition for mental hospital admissions. These opinions may be based on different patient populations and on institutions which function differently from those we investigated. An important implication of our finding, however, is that such assertions must be supported by systematically accumulated evidence.

Our results do not contradict assertions that clinics are keeping community persons from requiring hospitalization, but they do imply the importance of substantiation by control-group design. The problem is more easily stated than solved. Matching procedures are unlikely to equate patients on all relevant variables, including motivation for treatment and change, and situation at time treatment is attempted. Random assignment of patients to experimental and control groups faces two serious obstacles, which so far have not lent themselves to an entirely satisfactory answer: the ethical problem of withholding treatment from people who need it, and the reduction of the experimental group by patients who drop out of treatment.

The use of self-controls, that is, of the patient's previous adjustment history, in judging the effects of treatment is basically the clinician's own method of evaluation. Extensions and refinements of such case-oriented methods may be of particular value in this research area.

Apart from the problem of controls, it seems questionable to restrict a clinic study to the issue of the prevention of hospitalization. Hospitalization is but one of many relevant outcomes for seriously ill psychiatric patients. A study devoted solely to the question of whether clinics prevent hospitalization would fail to define treatment goals in terms of the varied functions of clinic treatment. Thus, despite the dramatic and tangible nature of such a demonstration, we believe that it would be more theoretically defensible and a more efficient use of observations to consider hospitalization as but one of the important outcomes to be studied.

Other research issues are suggested by the present study. The discontinuities between hospitals and clinics indicate the importance of research on experimental programs which bridge the gap between these traditional services, and also on significant processes which take place in the life of the patient when he is not under the direct care of either hospital or clinic.

Implications for Practice.—Analysis of unsuccessful referrals by the research staff and the hospital and clinic participants supports an interpretation that hospitals and clinics have largerly distinctive and, at least

occasionally, supplementary rather than identical and competing functions in the care of the mentally ill. Supplementary functions include brief periods of hospitalization in the course of clinic treatment of some very disturbed patients; outpatient clinic treatment of some patients released from the hospital; early detection in the clinic and referral to the hospital of severely ill patients, and early clinic treatment of psychiatric patients who would otherwise require hospitalization at some future time. These functions often are impeded in practice by the traditional separateness of hospitals and clinics, as exemplified by geographic distance and administrative isolation.

This interpretation suggests that closer liaison between hospitals and clinics, along both formal and informal lines, must be developed if patients are to receive the benefits of an integrated treatment that would allow ready transfer from inpatient to outpatient status, and vice versa.

The design of the study does not test the hypothesis that the patient could have benefited from outpatient care at some point before the decision for his hospitalization and therefore might not have required it. The results do indicate that once the patient has arrived at the hospital, outpatient psychotherapy is ordinarily not a practical alternative, because the problem has become one of restoration of the patient to the community, as well as of treatment.

The results suggest the merit of programs for patients who do not require full hospital care but are unable or unwilling to use the services of the community clinic.

Summary

An unselected sample of 504 patients in three state hospitals was evaluated for outpatient clinic suitability shortly after their admission. In all but 20 cases, referral to the clinic was not attempted because the patients were judged to have obvious need for inpatient care, or because their attitudes or those of their families discouraged a referral. Of the 20 cases referred, only 6 were accepted for treatment by the two participating clinics. Of the three patients who entered outpatient treatment, only two were judged by their therapists to have benefited from treatment.

The study emphasizes both the marked discontinuities in functions of the participating hospitals and clinics and the difficulties in initiating outpatient treatment with hospitalized patients shortly after their admission. It implies the importance of interventions prior to hospitalization and the value of services to bridge the gap between the traditional functions of hospitals and clinics for already hospitalized patients.

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Urinary Excretion of 5-Hydroxyindoleacetic Acid in Psychotic and Normal Subjects

Excretion After Parenteral Administration of Serotonin

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The hypothesis of Woolley and Shaw [1-3] that an altered metabolism of 5-hydroxytryptamine (5-HT), serotonin (Rapport [4]), or enteramine (Erspamer [5]) may be of importance in the genesis of a psychiatric disturbance, namely, schizophrenia, has aroused great interest and inspired countless investigations. We do not know whether it is a deficiency or an excess of serotonin that may be responsible for the abnormal brain function. In fact, the role played by serotonin in cerebral physiology has yet to be determined.

The possibility that the altered metabolism of an endogenous amine may play a role in the genesis of schizophrenia seems particularly interesting in view of the work of V. M. Buscaino.[6] For over 35 years this investigator and his school have pointed out that the only unquestionable changes found in schizophrenic patients indicate the existence of an altered metabolism of biological amines, including those derived from the indole nucleus.

Since the terminal product of the metabolism of serotonin excreted in the urine is 5-hydroxyindoleacetic acid (5-HIAA), we have undertaken a study of the daily excretion of 5-HIAA in schizophrenic patients and nonschizophrenic subjects in order to see whether such data would give any indication of an altered metabolism of serotonin in schizophrenia. The results of our investigations are reported in this paper, together with data on the pattern of urinary excretion of 5-HIAA after the parenteral administration of serotonin.

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Methods and Material

The urinary excretion of 5-HIAA was studied on 24-hour urine samples by three methods: (*a*) the color reaction according to Sjoerdsma, Weissbach, and Udenfriend,[7] as a qualitative index of the presence of 5-HIAA in the urine; (*b*) bidimensional paper chromatography according to Jepson,[8] to identify 5-HIAA and other indole derivatives, and (*c*) the quantitative determination of 5-HIAA in the urine by the method of Udenfriend, Titus, and Weissbach.[9]

The qualitative test was performed on the urine of 647 persons: 46 normal subjects, 265 neurological patients, 107 psychotic patients nonschizophrenic, 208 schizophrenics, and 21 subjects with cancer of the stomach. Paper chromatography was done on samples of urine of 272 subjects: 18 normal subjects, 72 neurological patients, 45 psychotic nonschizophrenic patients, and 137 schizophrenics. The amount of urine used for each chromatogram was 0.08 ml. Finally, the quantitative determination of the amount of 5-HIAA was carried out on the urine of 109 patients: 18 normal subjects; 22 neurological patients; 11 psychotic nonschizophrenic patients, and 58 schizophrenics.

The study of 5-HIAA excretion after the intramuscular injection of serotonin was done on 68 subjects: 10 normal subjects, 16 psychotic nonschizophrenic, and 42 schizophrenics. The rate of excretion of 5-HIAA before the injection of serotonin was determined by the three previously described tests on 24-hour urine samples. Fifteen milligrams of serotonin-creatinine sulfate was injected intramuscularly. Separate urine samples were collected at the first, second, fourth, and sixth hours after injection, and for the final

sample the urine excreted during the following 18-hour period was used. The excretion of 5-HIAA was then determined in each of the samples by the three methods described above.

Results

A. Qualitative Color Reaction.—In accordance with our previous experience[10,11] and trials made with varying dilutions of the pure substance, this qualitative test begins to give positive results when 5-HIAA is present in urine in concentrations of 25μg.-35μg. per cubic centimeter. At such values a pink or pink-purple color develops. With a concentration of 40μg/cc. the resulting color becomes frankly purple, and, as the concentration is further increased, the color changes progressively to a dark purple. In our study we counted as positives only those tests resulting in a shade of purple.

In our series the positive results were distributed as follows: in 4 out of 46 normal subjects (9%), in 52 out of 265 neurological patients (19%), in 21 out of 107 psychotic nonschizophrenic patients (19%), in 61 out of 208 schizophrenics (29%), and in 17 out of 21 patients with gastric carcinoma (81%). When the group of schizophrenic patients was divided into diagnostic categories of catatonic, simplex, hebephrenic, paranoid, and chronic regressed, it appeared that the highest incidence of positivity was found in the catatonics (40%) and the lowest in the chronic regressed (18%).

By grouping the schizophrenic patients according to the duration of the disease, we obtained the highest incidence of positivity in the urines of patients who had been ill for less than one year (41%). An increased number of positive results was also found among patients under various treatments as compared with those not treated. It must be said that the schizophrenics under treatment (EST, insulin, tranquilizing drugs) were also those who had been ill for shorter periods. The patients receiving chlorpromazine showed rates of positivity no different from those under other types of treatment. Our group did not include any subject treated with reserpine.

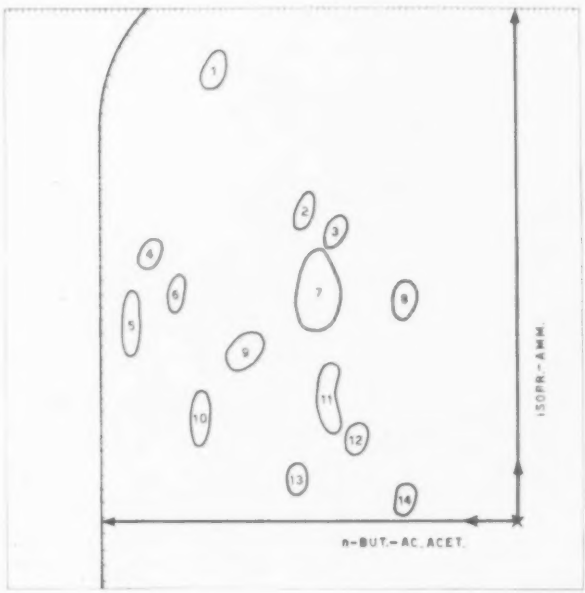

Fig. 1.—Sample chromatogram with spots for indole derivatives excreted in the urine (see description in the text).

1 indicates tryptamine; *2*, R_f 0.68-0.52; *3*, indoxylsulfate; *4*, acetyltryptophan; *5*, indoleacetic acid; *6*, indolelactic acid; *7*, urea; *8*, R_f 0.04-0.28; *9*, indoleacetylglutamine; *10*, 5-hydroxyindoleacetic acid; *11*, tryptophan; *12*, R_f 0.11-0.46; R_f 0.08-0.60 (U_2); *14*, R_f 0.02-0.40 (sulfuric ester of 5-hydroxyindoleacetic acid).

B. Chromatographic Studies.—A chromatogram, obtained from the urine of a schizophrenic patient and reproduced in Figure 1, shows the spots most frequently found in our study. The corresponding compounds are listed in the Figure.

Spots for serotonin and *N*-methyl-serotonin were not identified with certainty, probably because they do not separate distinctly from the spot with R_f 0.68-0.52. Spots for tryptophan, acetyltryptophan, indican, and 5-HIAA were found in the chromatograms of urine of schizophrenic patients as often as in those of control subjects. The spots for tryptamine, indoleacetic acid, and indoleacetylglutamine were observed less frequently in the schizophrenics than in the controls. A spot with R_f 0.40-0.28 (perhaps an end-product of purine metabolism) and an unidentified spot with R_f 0.68-0.52 were more frequently seen in the chromatograms of schizophrenics. A spot with R_f 0.11-0.46 (possibly methoxytryptophan) was found in the urine of 34 out of 137 schizophrenic subjects (25%) and did not appear in the chromatograms of urine from normal subjects. These spots were found more frequently in the acute schizophrenics (ill for less than one year) than in the chronic cases. No significant difference was noted when the chromatograms of patients under chlorpromazine treatment were compared with those of other schizophrenic patients.

Considering the frequency of appearance of the spot for 5-HIAA in the chromatograms of urines that had shown positive results by the qualitative test of Sjoerdsma and colleagues,[7] we found that in only 85% of such samples did the spot for 5-HIAA occur in the chromatogram.

C. Quantitative Determination.—All values will be expressed as milligrams of 5-HIAA per 24 hours. The determinations were made on 6 ml. of urine taken from the 24-hour sample. In 18 normal subjects the maximum concentration of 5-HIAA found was 9.2 mg. and the average was 5.15 mg. In 22 neurological cases the maximum concentration was 7.2 mg. and the average 3.9 mg. In 11 psychotic nonschizophrenic patients the maximum was 8.3 mg. and the average 5.1 mg. In 58 schizophrenics the maximum value was 26.0 mg. and the average 6.1 mg. Seven schizophrenic patients had values exceeding 9.2 mg., which is the highest absolute amount found in any nonschizophrenic subjects. In the schizophrenic group the catatonic patients appeared to have slightly higher amounts of urinary 5-HIAA (10 mg., average value). When the schizophrenic group was subdivided into acute and chronic, it was found that the acute group had higher values (8.3 mg.) than the chronic groups (4.2 mg.).

Summary and statistical analysis of the data are presented in the accompanying Table.

Summary of Twenty-Four-Hour 5-Hydroxyindoleacetic Acid (5-HIAA) Excretion

	No Schizophrenia			Schizophrenia		
	A Normal Healthy Subjects	B Neurological Nonpsychiatric Patients	C Psychiatric Nonschizophrenic Patients	D Noncatatonic Patients		E Catatonic Patients
Number	18	22	11	52		6
Mean 5-HIAA excr., mg. 24 hr.	5.15	3.90	5.10	5.64		10.01
Standard deviation	2.52	1.77	1.68	3.74		9.92
Standard error of mean	±0.60	±0.30	±0.51	±0.52		±4.44
	S. E. D.	N	t	P		
D+E *vs.* A	0.85	74	0.88	0.4	0.3	
D+E *vs.* C	1.36	67	0.23	0.9	0.8	
D+E *vs.* A+B+C	0.78	107	2.08	0.05	0.02 *	
D *vs.* A+B+C	0.66	101	1.77	0.1	0.05	
E *vs.* D	2.09	56	2.18	0.05	0.02 *	
E *vs.* A+B+C	1.17	55	3.21	0.001 †		

* These values are probably statistically not significant.
† This is the only value statistically very significant.

D. Urinary Excretion of 5-HIAA After Intramuscular Administration of 15 mg. of Serotonin-Creatinine Sulfate (Equivalent to 6.45 mg. of Free Serotonin)—1. Qualitative Color Reaction: In 12 out of the 68 cases of samples taken during the 24 hours following serotonin administration, the color test yielded the same result as in the urine collected on the previous day. In the remaining 56 cases the injection of serotonin determined the appearance of a positive reaction in cases which had been negative and an increase of the intensity of the color in those previously positive. Such changes became apparent in the samples taken one hour after the administration of serotonin. The positivity reached its maximum in the sample taken at the 2d hour, and then in most cases gradually diminished until, in the urine collected at the 6th hour, the reaction was the same as before serotonin and remained so in the samples collected from the 12th to the 24th hour.

No significant difference between schizophrenics and normal subjects was noted in comparing the results of this test.

2. Chromatographic Study: In 10% of all cases the results of the chromatographic analyses did not change after the administration of serotonin. The spot for 5-HIAA did not appear if previously absent, and, if present, remained the same in size and density. In another 10% of the cases a slight change in the appearance of the spot for 5-HIAA took place, consisting of a barely noticeable increase in size and/or density. The remaining 80% of the cases showed either the appearance of the spot for 5-HIAA when it had been absent, or a well-marked increase in size and density. As to the behavior of the spot, no difference was noted between the group of schizophrenics and other subjects.

A spot referable to 5-hydroxytryptamine was not identified with certainty.

In about 50% of the schizophrenics tested the spot of indoleacetic acid disappeared or became barely noticeable. A similar change occurred in the spots referable to tryptophan in about 33% of the schizophrenics.

3. Quantitative Determination: This was made in only 50 of the 68 cases in which serotonin was injected (9 normal subjects, and 5 psychotic nonschizophrenic and 36 schizophrenic patients). In 4 out of 50 subjects an increase of urinary 5-HIAA failed to appear. In the remaining subjects an increased excretion of 5-HIAA was found and was maximum in the samples collected two hours after the injection (in a few instances the maximum was reached at the fourth hour). In successive samples the concentration of 5-HIAA diminished progressively.

The total amount of 5-HIAA excreted in the urine during the 24 hours following the injection of serotonin was calculated for each subject; from that figure the amount of 5-HIAA excreted in the 24 hours preceding the injection (taken as a daily excretion control value) was subtracted. The recovery rate was calculated from the differences between the two values, taking into consideration that 6.45 mg. of serotonin had been injected and that the transformation ratio of serotonin to 5-HIAA is 0.92:1.0.

The averages of the recovery values, expressed as percentages of the amount of injected serotonin recovered as urinary 5-HIAA, were 25% in 15 normal and nonschizophrenic subjects and 42% in 36 schizophrenics.

In 3 out of 14 nonschizophrenic cases the recovery was more than 40% (42%, 51%, and 58%). In 19 of the 36 schizophrenics the recovery exceeded 40%, and of these 19 patients 3 had a recovery rate above 90%.

The rate of excretion of 5-HIAA, calculated in micrograms per hour, was significantly higher in the schizophrenics, especially during the first two hours after the injection of 5-HT (Fig. 2).

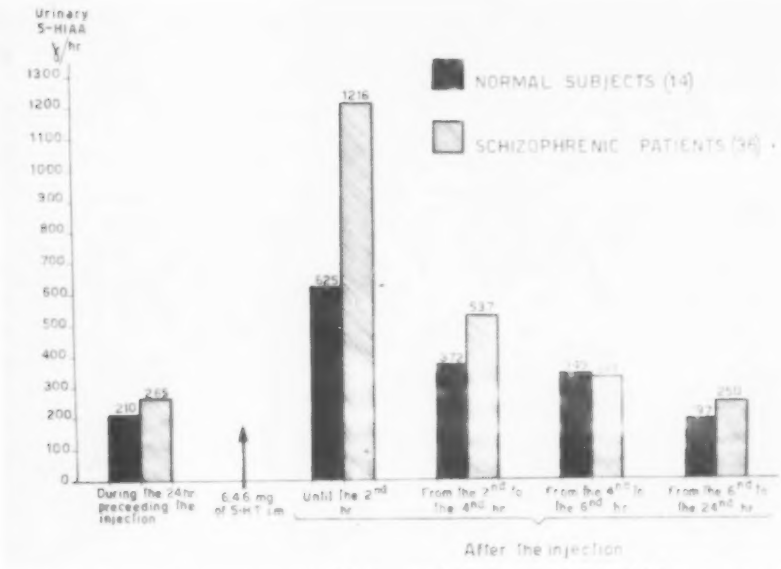

Fig. 2.—Rate of excretion of 5-hydroxyindoleacetic acid (5-HIAA), expressed as micrograms per hour, following injection of 5-hydroxytryptamine (5-HT). Graph obtained from mean values.

Comment

A. Daily Urinary Excretion of 5-HIAA.

Udenfriend and co-workers,[9] whose method we used, reported that in normal subjects the daily excretion of 5-HIAA ranged from 2 to 8 mg. In our series of normal subjects we found a maximum value of 9.2 mg., with an average of 5.15 mg., which agreed with the findings of Udenfriend and associates.[9] The averages of all groups, including the schizophrenic patients, were well within normal limits (Table). However, for the subgroups of catatonic patients and patients with acute schizophrenia, the values were near the upper limits of the normal variation. The few patients showing figures significantly higher than the upper limit of the normal range were all schizophrenics. Such values ranged between 18 and 26 mg. However, even in these instances the values were far below those observed in cases of carcinoid tumors (Snow et al.[12]; Udenfriend and co-workers[9]).

Erspamer[5] has indicated that the dietary intake of tryptophan influences the amount of 5-HIAA in the urine because an appreciable portion of the amino acid is metabolized via the 5-hydroxyindole route. Furthermore, Rodnight[13] has shown that ingestion of L-tryptophan produces significant increases in the urinary excretion of serotonin. We have done a study (unpublished) of the urinary excretion of 5-HIAA after the ingestion of L-tryptophan and have found increases in some cases. In view of such possible sources of variation, we may say that the schizophrenic patients did not differ substantially from the nonschizophrenic subjects as to the amount of 5-HIAA excreted daily with the urine.

Comparing the results of the qualitative test for the detection of 5-HIAA in the urine, on one side, with those of chromatographic identification of the substance and its quantitative determination, on the other side, we found a discrepancy. In some samples the qualitative test was positive, while a spot for 5-HIAA did not appear in the

chromatogram and the quantitative determination proved that the concentration of the substance was very low. Previous studies concerning the minimum concentration of 5-HIAA in a test solution capable of producing a color reaction by the method of Sjoerdsma and colleagues[7] had shown that, whereas a pale pink color might develop with concentrations of 5-HIAA of between 15μg. and 25μg. per cubic centimeter, at concentrations below 15μg. cc. the test was always negative. However, in our samples a frankly positive color reaction was found in urines that were shown to contain less than 10μg/cc. by the quantitative method. Therefore, we suggest that a weak positive qualitative test in the urine does not indicate the presence of 5-HIAA in concentrations above normal. Perhaps other indole compounds may be responsible for such positive results. We found a higher incidence of positive qualitative reactions in the acute schizophrenics. In these same patients a spot with R_f 0.68-0.52 and also a spot with R_f 0.11-0.46 (possibly methoxytryptophan) were frequently observed which were not present in normal subjects. The significance of such unidentified substances in the urine of schizophrenics and the question as to whether or not these substances are responsible for the positive qualitative reactions are problems requiring further investigation.

Our data show that if a modification of the metabolism of 5-hydroxytryptamine occurs in schizophrenia, it is not reflected in the urinary excretion of 5-HIAA. However, we cannot exclude the possibility that the alterations may occur only in the cerebral district of the metabolism of serotonin. In that case the change would hardly be reflected in the pattern of urinary excretion of 5-HIAA, of which only 3%, as Erspamer[5] pointed out, may be derived from the brain serotonin.

An incidental finding of our study is the high frequency of positivity (81%) found in subjects with gastric carcinoma. However, the intensity of the reaction is low when compared with that seen in urine from patients with carcinoid tumors. Similar observations have been reported by Clerc-Bory and colleagues[14] and by Snow et al.[12]

B. Patterns of Urinary Excretion of 5-HIAA After Parenteral Administration of Serotonin.—Our data have shown that following the administration of serotonin there are great variations in the patterns of urinary excretion of 5-HIAA. In at least 10% of the subjects no increase of excretion of the acid occurred, and in the other 90% the excretion was augmented. The recovery rates showed that in the nonschizophrenic subjects the excess of 5-HIAA appearing in the urine accounted for at most only 50% of the serotonin injected (average recovery 25%), which is in accordance with the results of Erspamer.[5] In the schizophrenic the recovery was higher, with an average of 42%, and in a few instances it was above 90%. These data indicate that only a variable fraction of serotonin follows a metabolic path which leads to the urinary excretion of 5-HIAA. It is also possible that there are other routes for the excretion of 5-HIAA, perhaps in the bile as part of a hypothetical biliary-enteric circle. Moreover, serotonin can be transformed into melanins.[15-18] Losses or transformations occurring in this manner would account for low values and failures to recover serotonin as 5-HIAA in the urine. In some schizophrenics the recovery rates were significantly higher, as though in these subjects the metabolism of serotonin preferentially took the path leading to the excretion of 5-HIAA in the urine. This finding may give significance to the evidence revealed by the quantitative determinations of 5-HIAA made before the administration of serotonin, for these were the same patients who showed a daily excretion of 5-HIAA that was slightly higher than the control subjects. Furthermore, it was in the catatonic and in the acute schizophrenic patient that paper chromatography showed the

presence of unidentified indole substances which did not appear in normals. Again, in the same types of patients the qualitative test showed a higher incidence of positive results, which, as we have said, might indicate the presence of indole metabolites different from 5-HIAA. All these findings can be interpreted as evidence for the existence of a subtle biochemical disturbance in the early stages of the schizophrenic illness. Not only may the metabolism of serotonin be affected, but that of indole compounds in general and of all biological amines, which in the work of V. M. Buscaino[6] and his school has been stressed as the chief pathogenic mechanism of the disease. It is not unlikely that the altered function of the amine-oxidase enzyme, shown to exist in schizophrenics by the researches of G. A. Buscaino,[19] of Birkhäuser,[20] of Takahashi et al.,[21] of Özek,[22] of Cartwright and coworkers,[23] of Leach and Heath,[24] of Akerfeldt,[25] and of Abood, Gibbs, and Gibbs,[26] may also favor the metabolism of 5-hydroxytryptamine to 5-HIAA.

Summary and Conclusion

The daily excretion of 5-hydroxyindoleacetic acid (5-HIAA) in schizophrenics does not differ significantly from that of nonschizophrenic subjects. If in schizophrenia there is a basic alteration of the metabolism of 5-hydroxytryptamine, it is not reflected in the amount of its end-metabolite, 5-HIAA, excreted in the urine.

Parenterally injected 5-hydroxytryptamine may appear in the urine as 5-HIAA. In nonschizophrenic subjects the recovery rate averages 25%, while in schizophrenic patients it averages 42%, with individual values higher than 90% in some acute schizophrenics.

Chromatographic study has revealed the presence of indole metabolites different from 5-HIAA in the urines of catatonic patients and of acute schizophrenics in general. Such metabolites are perhaps responsible for the high incidence of positive results in the qualitative color reaction, although the urinary concentrations of this substance are not increased. The results do not support the hypothetical existence of a primary disturbance of systemic serotonin metabolism in schizophrenia. The abnormalities found in some acute schizophrenics, especially the catatonics, are regarded as added evidence for an enzymatic disorder affecting the general metabolism of biological amines in the early stages of schizophrenia.

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The Patient and His Experiences in an Outpatient Clinic

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It is a well-known fact that patients vary with respect to the number of visits they make to a clinic. We observed in our clinic that approximately one-third of the patients come only once, one-third less than five times, and one-third continue for more than five interviews.[7]

In an effort to delineate some of the factors which determine how long patients maintain contact with the clinic, we decided to gather data about the patient, the therapist's reaction to the patient, and the interaction between the two. We prepared a schedule which elaborated on these three categories. We independently completed a schedule from the chart of each patient. All items were subsequently compared, and agreement between our scores was high. When there was a difference, the patient's chart was reviewed, and after discussion we were able to arrive at a judgment acceptable to both. We examined the charts of all patients seen in the clinic between July 1, 1955, and June 30, 1956, excluding only those patients who immediately after intake were referred to other agencies, hospitals, or physicians. The total number of patients seen during the year was 536, of whom 183 (34.1%) were referred elsewhere. A total of 353 charts were reviewed. We gathered *all* our data from face-sheet information and the initial and first treatment interviews of each patient. We restricted our investigation to the patients' early contacts with the clinic, not only because of the importance of the initial experiences for the subsequent course of treatment but also because we felt that they could serve as an adequate sample of the therapeutic interchange.

We have not attempted to evaluate the results of therapy, but it seems reasonable to assume that patients who visited the clinic more frequently are more likely to have a favorable therapeutic experience. We do not imply, however, that repeated visits necessarily mean that patients had an experience which was therapeutic for them.

Our clinic is part of a large university hospital. It is staffed primarily by residents in their second year of training. Referrals come from both the hospital and the community. Intake procedure varies, depending on the source of referral. Hospital referrals which come from wards, clinics, and the emergency room are seen in "open clinic." Open clinic is held on the same morning each week. After an initial interview with one of the psychiatric residents, the patient is presented to the open-clinic conference, where disposition is made. Unless hospitalization or referral to a social agency is indicated, the patient may either be transferred to "regular clinic" and assigned for psychotherapy or be followed in open clinic. Follow-up interviews in open clinic tend to be shorter than one hour and may be scheduled at intervals longer than once a week. The patient is followed by the same resident who saw him initially. This type of contact is considered to be maximally beneficial for patients who, either because of difficulty in communication or because of the nature of the psychopathology, cannot benefit from more regular therapy.

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TABLE 1.—*Grouping of Patients*

	Group	Patients No.	Patients Percentage
OC 1	Open clinic—1 visit	60	17.0
OC —5	Open clinic—less than 5 visits	37	10.4
OC +5	Open clinic—more than 5 visits	17	4.7
OC-RC —5	Open clinic to regular clinic—less than 5 visits	9	2.5
OC-RC +5	Open clinic to regular clinic—more than 5 visits	27	7.9
I 1	Regular intake—1 visit	32	9.1
I —5	Regular intake—less than 5 visits	26	7.4
I +5 TP	Regular intake—more than 5 visits; contact terminated by patient	46	13.0
I +5 T	Regular intake—more than 5 visits; contact terminated by mutual agreement	99	28.0
	Total	353	100.00

Patients from the community are either self-referred or referred by other physicians or agencies. Initially, these patients are seen by an intake social worker, unless there is an indication that the patient is a psychiatric emergency, in which case he is seen by a resident. Disposition is made at weekly intake conferences. The intake policy of the clinic is to offer treatment to a wide variety of ambulatory patients, and the vast majority of patients seen in regular intake are accepted for once-a-week psychotherapy.

The 353 patients included in this study represent all the patients who were offered treatment during the year. Before tabulating our results, we divided the patients into nine groups. The groupings depended on two factors: (1) the type of initial contact —open-clinic or regular intake, and (2) the number of contacts—one, less than five, and more than five. Patients who were transferred from open clinic to regular clinic were placed in one of two separate groups, depending on whether they maintained their subsequent contact for less or more than five interviews. The group of patients who was initially seen at regular intake and maintained their contact for more than five interviews was subdivided further, depending on whether they terminated their contact unilaterally or by agreement with the therapist (Table 1).

Findings

1. *Biographical Data.*—The biographical data which agree with the findings of several recent studies [2,5,8,9] can be summarized briefly. The patients who remained in treatment tended to be younger (20-39 years), were married or single rather than divorced or separated, had gone to school for more than nine years, and were skilled or professional persons. There were no significant differences in sex or religious affiliation between those who continued treatment and those who terminated treatment in less than five interviews.

Patients with a history of previous psychotherapy continued treatment longer than those who had not had this experience. Five or more consecutive interviews were accepted by us as previous treatment. Only 18.7%-23.1% of patients who terminated contact in less than five interviews had had previous psychotherapy, whereas 34.8%-54.5% of those who continued to be seen in our clinic had had previous treatment.

2. *Source of Referral.*—Source of referral determined whether patients were first seen in open clinic or regular intake (Table 2). Of the patients seen in open clinic, 76.7% had been referred from the various hospital clinics or the emergency room. On the other hand, 80.7% of the patients seen in regular intake were either self-referred or referred by private physicians.

Patients seen in open clinic tended to drop out of therapy much more frequently than those seen in regular intake. Only 28.0% of the patients referred to open clinic returned more than five times, while 72.0% referred to regular intake visited more than five times.

TABLE 2.—*Source of Referral*

First Contact with Clinic	Referral Source, % Self	Hospital Clinics Emergency Room	Private Physician	Other
Open clinic	10.0	76.7	3.3	10.0
Regular intake	57.1	0.5	23.6	18.8

TABLE 3.—*Diagnostic Data*

Diagnosis	Patients	
	No.	Percentage
Character disorders	140	39.7
Psychoneurotic reactions	88	24.9
Psychotic reactions	67	18.9
Adjustment reactions	20	5.7
Psychosomatic reactions	16	4.5
Brain disorders	1	0.3
Situational adjustment reactions	1	0.3
No diagnosis made	20	5.7
Total	353	100.00

3. *Diagnostic Data.*—"Character disorders" and "psychoneurotic and psychotic reactions" accounted for over 80% of the diagnoses made at the termination of contact with the patients (Table 3).

There were no significant differences in the diagnostic patterns among the nine groups. The only exceptions were the patients in the two open-clinic groups, who maintained contact for more than five interviews (OC +5 and OC-RC +5); the diagnosis for 35.0% of these patients was "psychotic reactions."

A specific recent stress which apparently precipitated referral to the clinic was identified in 63.0% of the patients, but this was not significantly related to continuation of treatment.

4. *Presenting Complaint.*—We classified the presenting complaints under four headings: psychological, somatic, situational, and mixed. Under "situational" we included vocational, financial, and housing problems, and under "mixed," psychological complaints which were presented in conjunction with somatic and/or situational problems (Table 4). The evaluation of the significance of the presenting complaint with respect to continuation of treatment is difficult. On the one hand, it is apparent that patients who remained in treatment were more likely to present their complaints in psychological terms; for example, open-clinic patients who after transfer to regular clinic continued in treatment had a significantly higher percentage of psychological complaints than all other open-clinic patients. On the other hand, it did not necessarily follow that because a patient had psychological complaints he would continue treatment. For example, among the intake groups there was no significant difference in the percentages of psychological complaints; yet some patients did not return after the initial interview, while others continued. The presence of somatic and situational complaints may be an important contributory factor. The percentages of such initial complaints were higher in the groups who did not return for more than five interviews, and this becomes even more apparent if the open-clinic and intake groups are compared separately.

The *severity* and *duration* of the illness did not vary significantly among the different groups. In the total patient population the illness was rated as "mild" in 20.1%, "moderate" in 49.0%, and "severe" in 20.9%. The duration of illness was more than one year in 76.2% of all patients.

5. *Attitude of Therapist.*—There were striking differences in the attitude of the therapist toward the patient (Table 5) and his evaluation of the patient's treatability (Table 6) in the groups of patients who dropped out of treatment and in those who continued. We rated the attitude of the therapist toward the patient as accepting, ambivalent, and nonaccepting, and his evaluation of the patient's treatability as positive, doubtful, and negative. It is of interest that, on the whole, the patients who were acceptable to the therapist, and whom he

TABLE 4.—*Presenting Complaint*

Group *	Presenting Complaint, %			
	Psychological	Mixed	Somatic	Situational
OC 1	26.7	11.6	46.7 †	15.0 †
OC −5	18.9	32.5	35.1	13.5
OC +5	29.6	29.6	35.0	5.8
OC-RC −5	11.1	22.2	66.7	0.0
OC-RC +5	55.6	18.8	22.0	3.6
I 1	65.8	21.7	8.3 †	4.2 †
I −5	61.5	3.9	26.9	7.7
I +5 TP ‡	60.9	34.7	4.4	0.0
I +5 T §	73.7	19.2	5.1	2.0

* OC indicates open clinic; RC, regular clinic; I, regular intake.

† The percentages of somatic and situational complaints would have been considerably higher had the patients who were referred elsewhere been included in this study.

‡ Contact terminated by patient.

§ Contact terminated by mutual agreement.

TABLE 5.—*Therapist's Attitude Toward Patient*

Group *	Therapist's Attitude Toward Patient, %		
	Accepting	Ambivalent	Nonaccepting
OC 1	53.3	15.0	31.7
OC −5	62.1	8.1	29.8
OC +5	64.7	11.8	23.5
OC-RC −5	33.3	33.3	33.3
OC-RC +5	77.8	22.2	0.0
I 1	75.0	6.2	18.8
I −5	65.4	15.4	19.2
I +5 TP	76.1	13.4	10.5
I +5 T	86.9	10.1	3.0

* OC=open clinic; RC, regular clinic; I, regular intake; TP, termination by patient; T, termination by mutual consent.

TABLE 6.—*Therapist's Attitude Toward Treatability*

Group *	Attitude Toward Treatability, %		
	Positive	Doubtful	Negative
OC 1	21.7	36.6	41.7
OC −5	40.5	40.5	19.0
OC +5	29.4	64.7	5.9
OC-RC −5	22.2	55.6	22.2
OC-RC +5	81.5	18.5	0.0
I 1	40.6	28.1	31.3
I −5	57.6	30.9	11.5
I +5 TP	58.7	34.8	6.5
I +5 T	83.8	14.2	2.0

* OC=open clinic; RC, regular clinic; I, regular intake; TP, contact terminated by patient; T, contact terminated by mutual agreement.

felt could be treated, stayed in treatment irrespective of whether they were seen initially in open or in regular clinic. This was most convincingly demonstrated by the intake group which terminated treatment by mutual agreement (I +5T) and by the open-clinic group which was transferred to regular clinic and visited for more than five interviews (OC-RC +5). The therapist felt positively about treatment toward more than 80% of these patients. The therapists were considerably less optimistic about the treatability of patients in the other groups.

6. *Attitudes of Patients.*—We evaluated both the patient's interest in treatment (Table 7) and his feelings about and expectations from treatment. Interest was rated on a three-point scale, varying from clearly expressed interest to no interest. There is a high correlation between the patient's interest in treatment and length of contact with the clinic. *In fact, this turned out to be the best single indicator of the patient's length of contact with the clinic.*

Attitude toward treatment was judged as fearful, hopeful, desperate, magical, aggressive, and skeptical. Among the patients who continued treatment there was more expression of hopefulness, as well as fearfulness, about treatment, while the other attitudes predominated in the patients whose contact was briefer.

Although the attitudes described above could be inferred in each case from reading the record, we found that in relatively few cases did the therapist deliberately focus on these attitudes as they related to treatment (Table 8). Those patients with whom the therapist explored these feelings tended to return to the clinic for longer periods.

7. *The Therapists.*—More than 80% of the patients included in this study were seen by nine psychiatric residents; the rest of the patients were treated by social workers,

TABLE 7.—*Patient's Interest in Treatment*

Group *	Patient's Interest in Treatment, %		
	Clearly Expressed	Had to Be Encouraged	Little or No Interest
OC 1	11.7	16.7	71.6
OC −5	27.0	32.5	40.5
OC +5	29.4	35.3	35.3
OC-RC −5	33.3	44.5	22.2
OC-RC +5	66.7	18.5	14.8
I 1	34.4	28.1	37.5
I −5	23.1	34.6	42.3
I +5 TP	60.9	30.4	8.7
I +5 T	87.9	11.1	1.0

* OC=open clinic; RC, regular clinic; I, regular intake; TP, termination by patient; T, termination by mutual agreement.

TABLE 8.—*Exploration of Patient's Feelings About Treatment*

Group *	Exploration of Patient's Feelings About Treatment, %			
	Considerable	Moderate	Minimal	None
OC 1	0.0	1.7	6.6	91.7
OC −5	2.7	5.4	10.8	81.1
OC +5	0.0	0.0	11.8	88.2
OC-RC −5	0.0	0.0	11.1	88.9
OC-RC +5	3.7	11.1	18.5	66.7
I 1	0.0	15.6	25.0	59.4
I −5	0.0	3.9	15.4	80.7
I +5 TP	6.5	6.5	15.3	71.7
I +5 T	13.1	18.2	24.2	44.5

* OC=open clinic; RC, regular clinic; I, regular intake; TP, termination by patient; T, termination by mutual agreement.

psychologists, and medical students, all under supervision. The average case load was about the same for each resident during the year. A most striking finding was that the drop-out rate of patients was about the same for all residents except one. This resident lost about three times as many patients as the rest of the group, and from the outset he appeared to have the most difficulty in establishing rapport with his patients. There was only a slight tendency among the more competent residents to bring more patients to mutually agreed termination. We also noticed that some residents tended to keep the patients in treatment longer than others, but since in this study we limited ourselves to whether patients came for less or more than five interviews, we could not substantiate this further.

8. *Drugs.*—Drugs were rarely used (10.2%), and were usually given to patients in open clinic. The sample is too small to allow for definite conclusions; we can only speculate that perhaps the drugs helped to keep some of these patients coming to the clinic.

Comment

Our findings that patients of higher social status seek psychotherapy more frequently and continue treatment longer are in agreement with the reports of other investigators.[5,8,9] Since higher social status is correlated with vocational and educational achievement, patients with greater attainment in these areas remain in treatment longer.

Of importance in determining the length of contact with the clinic was the patients' capacity to express their complaints in psychological terms, to refer themselves to the clinic, to want treatment, and to be hopeful about it, though not unaware of its difficulties. In contrast, patients whose contact with the clinic was brief, had somatic or situational complaints, were referred by others, and were skeptical about treatment. Most of these patients did not recognize their anxiety or their own participation in the problems they presented. They tended to approach the therapist with the expectation that a magical solution for their difficulties would be forthcoming. It was striking that many patients who continued treatment expressed a great deal of anxiety about it in their initial contacts. The finding that a significantly larger percentage of patients who remained in treatment had had previous psychiatric contact may be related to this. It is our impression that some of these patients were able to accept treatment, because anxieties about treatment, while still present, had at least been somewhat allayed by a series of preliminary trial contact with therapy. It may be that an optimal level of awareness of anxiety facilitates treatment. Of course, others returned for additional treatment because they had found previous contact helpful. In general, patients who maintained contact with the clinic were able to recognize their psychological difficulties and communicate with the therapists in these terms.

Other investigators[2,8] have also observed that the ability to recognize emotional stress and communicate it verbally, rather than by somatization, is characteristic of persons who seek and proceed with psychotherapy. The appeal of these patients is related in part, at least, to this capacity, which is valued by psychotherapists and plays so important a part in their professional functions. Schaffer and Myers[10] have shown that the bias of the therapist affects the selection of cases, and Redlich, Hollingshead, and associates,[5] and Freedman and Hollingshead[3] have pointed up many subtle factors related to social class which influence both the course and the availability of treatment. Although the capacity for psychological awareness is neither restricted to nor found universally among persons of higher social status, it is more frequent in these groups. Whether this psychological orientation is developed by virtue of belonging to a social class which places a premium

on it, or whether it is a personality variable of importance in determining into what class a person settles, is not clear. Upward social mobility appears to be associated with a striving for the values of the group,[6] and it may be that persons who seek higher social status are partially motivated by a wish to associate with those who appreciate psychological processes. Although an awareness of psychological factors is necessary, it is not sufficient for continuation of treatment, as many patients who expressed themselves psychologically did not maintain their contact with the clinic.

The length of contact the therapists had with their patients varied. Some residents tended to see their patients fewer times than others. Although we have no conclusive data, it is our impression that the more competent residents maintained longer contacts with their patients. Since "the number of contacts" beyond five was not investigated, the difference was not striking; and, with the exception of one therapist, probably the least competent in the group, who lost many patients, the rate of continuation was about the same for all. While it was apparent that the patients who were acceptable to the therapists and considered treatable by them continued treatment, we wish again to emphasize the patient's contribution to treatment, as patients continued treatment with each of the therapists, whereas other patients did not return even to the most competent therapists. The correlation between the patients' clearly expressed wish for treatment and the continuation of therapy is impressive. The correlation was higher than with any other single factor included in this study.

Rosenbaum et al.[9] stressed that less experienced therapists lost more patients; but if patients continued treatment, as many were likely to improve with less experienced as with more experienced therapists. Miles et al.[8] reported a slightly higher rate of improvement with more skilled therapists. Frank et al.[2] reported variations among the psychiatrists in percentage of patients who left therapy, but found no striking correlation between therapist's experience and knowledge and outcome. The patients' contribution to treatment may, in part, explain the difficulties in evaluating various psychotherapeutic procedures. Patients respond to a variety of therapeutic techniques, and it is often difficult to identify the factors which are crucial to a successful outcome. It may be that some patients are so eager for and receptive to the type of relationship provided by therapy that technical variations matter little, and they respond favorably to many different approaches. It is likely that the skilled therapist, by virtue of his greater understanding, makes of therapy a more significant and meaningful experience. Therefore, it seems important that future studies address themselves to an evaluation of the changes brought about by "successful" treatment, rather than a comparison of the results of a variety of therapeutic techniques or of different therapists. Such an approach is also suggested by the frequently encountered statements that different therapeutic techniques give similar results.

The importance of the recognition of the patients' feelings about treatment has been stressed by Coleman[1] and Gill et al.[4] We found this mentioned in relatively few interviews, but it occurred more frequently in the interviews of those who continued treatment. It may be that the mention of this in the record reflected an orientation of the therapist which helped to make treatment a more meaningful experience, and so the patient returned to the clinic, or, again, it may be that some of the patients, because of their own psychological awareness, introduced these feelings in the interview and that continued contact was due to their own psychological aptitude. It is most likely that both of these factors operate and that the ideal therapeutic situation develops when both patient and therapist are sensitive to psychological nuances and are able to communicate them. The therapists' ability to understand and respond to patients' stresses, even though covertly expressed, facilitates

treatment. Although many factors influence continuation of treatment, two very significant ones may be the patients' readiness for the experience of treatment and the therapists' ability to share this experience with them. To the treatment experience are brought many attitudes and feelings which are characteristic of the patients in many other interpersonal situations; and as these develop and are identified in treatment, the patient becomes more able to cope with them.

Summary

We have reviewed the charts of all patients who were seen in the outpatient clinic for one year in an effort to delineate the factors which determine continued contact with the clinic. We completed a schedule, relevant to treatment, which enumerated items about the patient, the therapist, and the interaction between them.

We found (*a*) that patients who continued treatment were aware of the psychological nature of their problems and were able to communicate in these terms; (*b*) that therapists liked and felt hopeful about treating those patients who subsequently remained in treatment, and (*c*) that continuation of treatment is dependent upon attributes of both patient and therapist, but that the patient's desire and readiness for treatment plays a very decisive part.

The therapeutic interaction of patient and therapist deserves further investigation, as we have little definitive knowledge about its effects on the continuation of treatment.

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Hallucination as an Ego Experience

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Like any psychiatric phenomenon, hallucinations can be examined and studied in a variety of ways. Many writers, most notably Bleuler, have presented detailed descriptions of them. Others have debated the issue of images of special intensity *vs.* perceptions. Theories have been propounded to explain their origin, and these have ranged from oversensitivity of certain areas of the brain to disowned wishes returning in disguised form and as though they arose from an outside source. Content has been scrutinized in terms of superego activity and as an attempt to reestablish object relationships. The attention of clinicians has been engaged by the significance of a cultural norm in determining what is and what is not a hallucination. The prognostic implication has also been a matter of interest. While this by no means is a complete list, it indicates the diversity of approaches to this subject.

The purpose of this article is to view hallucinations in still another way. Our attention will be engaged by the inner experiences of the patient. How is the hallucination first perceived? And what are the later reactions to it?

Steckler [1] studied the initial response to hallucinations. He noted that it was always one of extreme fear, often accompanied by autonomic nervous system concomitants (rapid heart action, palpitation, hyperhidrosis, etc.). Invariably the patient thought that the experience meant that he was "going crazy" or "losing his mind." He would immediately rush to a relative, a physician, or a clergyman for reassurance.

It is commonly stated that the patient reacts to the voices he hears or the visions he sees with "unshakable conviction." [2] The experience in which "unshakable conviction" is lacking is referred to as pseudohallucination.[4] Our observations lead us to contend that hallucinations and pseudohallucinations are points on a continuum rather than two distinct entities. Often the observing function of the ego remains sufficiently intact to scrutinize the affective experience, much as an outside observer would.

After the initial experience—if the hallucination persists—an adaptation is made to it. This consists of an effort to reconcile the inner experience with the ego's accustomed (or former) way of viewing the world.

Method of Study

Our data were gathered from two groups of patients who had been diagnosed as schizophrenics. The first was comprised of relatively "acute" cases admitted to two hospitals providing short-term care. The second consisted of "chronic" cases at a state hospital (Marcy State Hospital). The groups were approximately of equal sizes, 12 and 13 patients, respectively. The interviews were tape-recorded.

Clinical Data

The thesis which has been stated above might be illustrated by either case histories or vignettes. In the interest of maintaining the focus on the most pertinent data, only the latter will be presented.

One patient, while hallucinating, attempted to determine the source of the

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voice he heard by plugging his ears. He commented: "Why, if it was coming from somebody talking, I wouldn't have heard it if I had my ears plugged up. So I checked that one on myself." He also stated: "Yes, you can hear them with your ears plugged. And then that's how I knew it was all in my mind instead of, say, coming from outside somewhere. I thought of doing that. It gets you after a while. It's just like actual talking and it really isn't, but still it seems the same. It's very confusing." Checking in this way to determine whether the voices are "inside" or "outside" is by no means uncommon. Many psychiatrists who work with large numbers of psychotic patients have encountered it.

The patient just quoted stated that a voice told him to kill himself. During his second psychotic episode, he went to a police station to ask for help to protect himself from the commands of this voice.

In this instance the observing portion of the ego clearly struggled with the hallucinations.* An attempt was made to localize the source of the voices by testing (plugging the ears). As an outside observer might, the patient concluded that the voice was "inside" rather than "outside." Since he felt unequal to the task of opposing the commands of the voice, even though he recognized its general source, he sought help from the police. (The dynamic implications of this struggle will not be discussed here, since they are beyond the scope of this presentation.)

Another patient referred to his auditory hallucinations as "thoughts." When asked about voices, he stated: "Do I hear voices? Yes, I have heard them, and I do hear them right now." When asked the source of the voices, he stated: "I imagine it's right from my brain." He enlarged on this later: "Well, you feel as if you're hearing it, but it isn't. There's a difference. You can tell when it's a voice and when it's a thought going through your brain. When it's a voice, it's clear-cut; and when it's a thought, it's more or less a little muffled. There's a difference." This man referred to his "voices" as telepathy. When he was asked whether telepathy was unusual, he responded: "Why, yes, of course, it's unusual. I imagine that's one of the reasons why you have me up here." When he was asked whether he felt it was unusual, he answered: "No, I'm not saying that, but that's your feeling. That's the feeling I get that you have."

It should be noted that he correctly identified the reactions of others to the phenomenon he experienced. It was as though the observing portion of his ego could no longer view the experience critically, but it retained the ability to comprehend how others would view it. He could infer that the hallucinations were an indication (to others, if not himself) that he needed to be hospitalized (i. e., that they meant that he was "crazy").† In this instance telepathy represented an attempt to reconcile the inner experience with the ego's former orientation.

Another patient stated: "There's nothing wrong with me. I'm O. K., except I hear some voices every now and then. That's about all. You know, if I could have an x-ray of my head, Doctor?" He suggested that there was "something wrong with my brain or something like that." The voices made him feel "nervous and upset." He added: "I figured if I was hearing voices maybe I was nuts or something." This man recognized the implications of the auditory hallucinations, and he provided a

* Hallucinations may be an ego experience and as such might be referred to as the participating ego, as contrasted with the observing ego. Or, as suggested by Weiss,[6] they may be the contents of the repressed id which force their way into consciousness, reaching the awareness of the ego.

† It is not uncommon for the patient to describe his hallucinations and state that they mean that he is "crazy" or "sick." One woman, when asked if she could distinguish "outside" from "inside" voices, answered: "Sure, I'm not *that* crazy!" It is as though there are levels of "craziness." The process would be more profound if it became impossible to differentiate what is internal and what is external.

theory (brain pathology) to account for them.

Another patient stated: "I could hear her, or I thought I could hear comments people had to say. I don't know, I thought it was—I explained it to myself—rather unusual hearing. Perhaps because of my poor eyesight, my hearing was better than average, and any comments on the subject tended to—in my mind, anyhow, maybe they didn't actually, maybe I only imagined it—tended to make my hearing and perception even greater when I was the subject of discussions, and I seemed to hear quite a few comments to the effect, 'Boy! he has it bad; he'll learn'; 'he's hurt; you can see it in his eyes,' and things like that." Later he said: "It was pretty unbelievable. I kept thinking I must be crazy or something. I figured I was in a pretty good place for it." Retrospectively, he stated that the voices were "real" when he heard them, but that when he did not they were "pretty unbelievable."

There were brief periods when the experience of hearing voices occupied almost the whole stage. As soon as they stopped, the observing portion of the ego came to the fore. (There was this alteration rather than a more delicate balance or almost simultaneous functioning of the two.) At such times he attempted to reconcile the two contradictory views (voices were heard *vs.* voices should not be heard in the absence of outside sounds). To do this, he devised a theory that he had unusual hearing.

Even in the face of extremely bizarre hallucinations, some attempt may be made to reconcile the voices with the observing ego's view of the world. A patient who maintained: "Well, I was only telling it like Jesus and God said, but I remember way back to the crucifixion," attempted to explain things by referring to Joan of Arc.

The patients whose vignettes have been presented all were seen at the "acute treatment" hospitals. The following group was interviewed at a state hospital.

The first patient, in commenting on the voices she heard, stated: "I can't say where it comes from. All I know is I hear it." The second patient said: "I believe in mental telepathy, but I have no mental illness." When asked whether imagination had anything to do with the voices, she replied: "Reality is reality." The third patient stated that it was not unusual to hear voices that come from a great distance. Her explanation was this: "I said I was the first God, didn't I? My husband is a God, too." These three patients had been hospitalized for periods ranging from 5 to 10 years.

A fourth patient, who had been in the hospital for 22 years, stated that his voices were due to the overflow of "electronic air." When a fifth patient was asked if her experience was unusual, she responded: "Why is it unusual? It's the real thing. . . . No, I wouldn't think so. He lives with her, and she comes up with him on Sundays. That's all there is to it. When I was over in that other building . . . he was in on that, fixed me up so that I wouldn't menstruate."

A sixth patient stated that her brother was hidden underneath the floor ("and that's the truth"), and that he spoke to her. She also maintained that the doctors and other employees could hear him. In this instance, the patient spoke of validation for her experience, but the observing, as well as the experiencing, ego was enmeshed in the process.

A seventh patient, who had been in the hospital for 17 years, stated: "They [the voices] disturb me. I can't understand why I should hear them and not pay any attention to them. They don't frighten me exactly. I wonder why we talk. For a while they may be all right, and then it would be that if I didn't obey them I would be a lost soul. It's hard to obey them; so I feel as if I'm a lost soul most of the time."

An eighth patient, who had been in the hospital only two months, after describing how she had been in a "daze-like state,"

stated: "I'm much better now. I don't know whether I hear things from the dead or from the living. Do you believe in hearing from the dead? Maybe it was imagination." She also attempted to explain her experience: "When you hear from the dead, they want you to die, too, don't they, or something like that? Or else, they're not resting in peace or something." She continued: "I don't think that I'm crazy, because not everyone is crazy when they say they hear someone. . . . Sometimes people are close to each other or something, and they can feel or hear something from them." Still she concluded: "Well, when they sent me here, I figured I must be crazy."

In this instance the patient, whose case was similar to the "acute" cases seen at the other hospitals, seemed to be emerging from a state in which the intensity of her experience was such that little observing of it was possible. She had now reached the stage of questioning—of standing off to some extent. There was an effort to bring an explanation to her experiences by "loosening" the process of validation.

Comment

A continuum exists with the type of commonplace event in which a person "imagines" he hears voices but the notion is quickly dispelled when he discovers a creaking floor board, at one extreme, to an unshakable conviction that he hears voices, at the other. Pseudohallucinations can be redefined as a point along this continuum.

Our attention, in this study, has been engaged by the ego's own reactions. Clearly, it is not always at one with the hallucinated experience. The initial response is that of fear bordering on panic. To some extent this state may persist for a considerable period of time and is responsible for much of the anxiety (and perhaps depression) noted in acute schizophrenic episodes. To an extent the ego maintains its observing function and reacts to its own experience (the hallucination) as something foreign, strange, or "crazy." Sullivan [6] referred to this feeling as uncanny. Much the same reaction may occur to other altered ego states, such as depersonalization, derealization, and a profound feeling of estrangement.

There are times early in the process when, for all practical purposes, the hallucinations are so intense or the observing power of the ego is so paralyzed or inoperative that "unshakable conviction" exists. In a sense, it might be said that the observing ego is then unable to maintain sufficient detachment for self-scrutiny. This state may occur for brief periods (less than a day) or for more sustained periods (more than a week), or it may be a fluctuating phenomenon.

In most instances, during the early stage, the observing function of the ego is maintained, at least to an extent. In speaking of delusions, Macalpine [7] stated: "It seems that there is an incipient stage in which the mind is wrong, yet still right enough to recognize that it is wrong." Hallucinations during this stage are viewed as "crazy." Bleuler [8] stated: "Often they [the patients] openly admit that they are afraid to reveal their experiences because these will be considered pathological and they themselves will be judged 'crazy.'" The use of the word "crazy" denotes the discrepancy between the experience and accustomed ones and the awareness of what others will think. It, also, in some measure serves as an explanation.

The patient's struggle to understand the nature of his experience is illustrated by the man who plugged his ears to determine whether the voices came from inside or outside. Another person differentiated between "thoughts" (hallucinations) and conversations. If it is maintained that hallucinations are held with "unshakable conviction," it follows that the patient's response would be that of uninquiring resignation. Clearly, this is not always so.

Thus far, we have discussed the responses which precede attempts to reconcile

hallucinations (which persist) with the ego's accustomed way of viewing the world. In most instances, an effort is made to bridge these two incompatible views. This can be achieved by making the hallucinations consonant with the order of things (as Freud [8] described Schreber's way of coping with his delusional system). To bridge, logical thinking usually must be abrogated and belief (in the religious sense) substituted. In other words, the usual process of validation must be suspended. Hallucinations are regarded as true (in the sense of affective truth—they feel right, so they are right). They now are fitted into the ego's previous orientation by the use of a variety of theories, often mystical in nature. In the cases studied this included "something wrong with my brain" (the only theory which adhered to logical thinking in a conventional sense), increased hearing, radio frequencies, telepathy, and special, religiously fostered powers (God's way, voices of the dead, etc.). When this type of reconciliation has occurred, the hallucinations are no longer regarded as "crazy." So to speak, they now make sense. It is at this point that "unshakable conviction" occurs.‡ (After a period of time even the need to reconcile may not be evident, as in the patient who stated, "All I know is I hear it.")

The process, as described, is one proceeding from an acute phase, in which an active struggle is waged, to a chronic phase, in which reconciliation occurs and harmony is restored. As in any struggle, the balance may shift at any point and a reversal follow. Thus, in patients who recover, the stage of reconciliation may be absent or short-lasting. (This may determine whether or not—or how much—"scarring" results from the psychotic episode.) At any rate, the hallucinations cease, and the ego's previous way of viewing the world once again, more or less, prevails.

‡ As previously noted, it may also occur during the "acute phase" if the experience is extremely intense or if the observing function of the ego becomes inoperative.

Summary

In this article, hallucinations have been viewed in terms of the inner experience of the patient. The initial reaction was one of extreme fear and the notion of "going crazy." For a brief period, the observing function of the ego often remained intact and scrutinized the affective experience as an outside observer would. Later—if the hallucinations persisted—an adaptation was made to them. This consisted of an effort to reconcile the inner experience with the ego's accustomed (or former) way of viewing the world. To accomplish this, the usual process of validation was suspended, and a variety of theories, often mystical in nature, were substituted.

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Experience of Perceptual Distortion as a Source of Anxiety

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Important in psychological growth is the emergence of cognitive functions through which external events are apprehended more in terms of perceptual field characteristics and less as outward representations of inner drive processes. As Freud originally proposed,[4] and Rapaport has recently developed at length,[14] the trend from primary toward secondary process thinking —from chaotic, or instinct-determined, cognition to reality-oriented, logical thinking— parallels the organism's maturing ability to delay discharge and gratification. Without such ability, there could be no concern with external events mainly in their own terms. In this conception, veridical perception serves a distinctly adaptive function, summarized in the phrase "reality testing." With the accretion of experience, and the operation of memory and an extended time perspective, the individual is able to act vicariously, i. e., to fantasy the conditions and consequences of action, rather than acting directly, as in an earlier stage. Hence, the sometimes painful consequences of error can be avoided. However, reality-oriented perception and logical thought are maintained not only bcause they serve adaptive function, but because of an equally important need for a stable conceptual world. Not only does the individual need to know what is external to him in order to deal better with it, but he needs simply *to know* an organized and meaningful world. This motivated aspect of perception has been expressed in such concepts as Bartlett's "effort after meaning" [2] or Tolman's "placing" need.[16] According to Murphy,[10] "The ordering of events in time and space gives satisfaction."

In psychopathological states the hard-won capacity for organized perception of the outer world, both social and physical, is reduced or perhaps never attained. The mobilization and maintenance of focal attention, figure-ground patterning, conceptualization, and other "higher mental processes" are impaired. Paralleling this, perception and thinking are invaded by affective processes, so that those ego functions which are relatively autonomous in the mature adult are again determined by inner needs in the mentally ill patient. In general, disturbances of cognition are related to three distinguishable, though often sequentially related, processes: 1. There is primary weakening of the integrative functions of the ego. 2. Affective and drive processes, exceeding the ego's controlling forces, are released directly into experience. 3. Defensive maneuvers, intended to prevent or minimize such invasion, themselves reduce perceptual accuracy by requiring the

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exclusion, distortion, or personalistic interpretation of experience. Moreover, even when successful in preventing anxiety, the exaggerated ego defenses of neurosis almost of necessity reduce the flexibility of behavior. The familiar, with which the individual has developed means of dealing, is sought, while the novel or uncertain is potentially dangerous and hence avoided. Thus, spontaneity and exploration necessary for creative thought cannot be tolerated. Even when distortion does not occur, thinking becomes simplified or trivial.

Anxiety as an affective state is related to the regression of cognitive functioning both as cause and as consequence. That free anxiety, in the intensities found in the mentally ill patient, can lead to the primitivation or rigidification of reality-appropriate judgment has been described in its many aspects in an extensive clinical and experimental literature. On the other hand, anxiety can arise as a direct consequence of the recognition of inability to organize, comprehend, and thus to respond appropriately to a complex stimulus world. With the loss of ego control, the danger of being overwhelmed by unmanageable stimulus input leads to anxiety. This mechanism is seen in relatively pure form in the brain-injured patient's "catastrophic reaction," described by Goldstein.[5] This condition is analogous conceptually to the experienced inability in dealing with repressed drives, which has been of more interest in the past in psychoanalytic theory. The threat is one of a loss of mastery; in the one case with respect to external, and in the other to internal, events, with anxiety signaling inadequacy in maintaining control.

This paper reports an experimental attempt to alter the anxiety level of patients and normal subjects by exposing them to a stimulation in which the adequacy of their perceptual judgments about quite simple external events was challenged. In brief, visual materials were presented for judgment, and again for more detailed examination, to test the correctness of the initial judgment. However, unknown to the subject, the materials were altered between the first and the second viewing, so that it seemed as though perception were inaccurate and, at times, projective. The effects of this "perceptual distortion stress" on emotional behavior and selected aspects of psychosomatic functioning were investigated. This experiment is one of a series concerned with the psychosomatic organization of anxiety which share a common experimental design, involving continuous or repeated measure of a variety of affective, psychological, physiological, and endocrine functions during experimentally produced stress conditions.[6]

In earlier experiments, the subject was confronted with emotional problems largely unresolved or denied, in a way which forced into consciousness large amounts of undigested self-knowledge. As we have noted earlier,[7] that this technique did not always produce anxiety demonstrates the effectiveness and speed of ego defense. However, the purpose was to produce some exprience of loss of control over inner impulses. In some cases, the unacceptable impulse was stimulated directly by the behavior of the interviewer, rather than through the verbal transaction and the interpretations made. In contrast to the stress interview, which can be characterized as an effort to reduce the certainty of control over inner events, and thus to lead to anxiety, the present experiment can best be described as threatening the ego's control of external events because of their misperception. Ultimately, the effect of the two conditions should be the same, but different aspects of ego control are attacked. Clearly, the distinction can never be absolute; but in a broad, though important, way the two stress conditions can be conceived as specific to the two major directions of ego control—in one case, with regard to the management of internal impulses, in the other, focusing on control of external reality.

Certainly, the two experiments differ in the mechanisms used to produce stress. In

the interview, the patient meets another human being in face-to-face social interplay, and the emotional consequences depend on the convincingness of the transaction for conveying the essentially unresolved nature of many of his problems. In the perceptual situation, by contrast, the primary transaction is between the subject and the perceptual materials, with the emotional impact deriving from the perceived incongruity, rather than depending on the social interplay. Consequently, the role of the experimenter is more that of "examiner" than of "stresser," as in the interview condition.

Procedure

General Experimental Design.—The study consisted of four consecutive days. On the first of these ("preexperimental day") the subject was brought to the laboratory and the various psychological, physiological, and biochemical measures made, without, however, any explicit stress being introduced. This day was intended to familiarize the subject with the laboratory and the test procedures, although, as noted in the report of the earlier experiment,[18] it was for many subjects a rather formidable experience and cannot in any sensible way be considered a "basal" condition. The stress was introduced in each of the following three experimental days (Days 1, 2, and 3). On these days, the same set of measurements was made in the period before, during, and after the stress. In all cases, however, indices of performance are available for all of the major periods of the total experiment: preexperimental day, and pre- and poststress on each of the three experimental days.

This paper is intended mainly to present the experimental stress technique—to describe the procedure, its meaning to the subjects, and its emotional consequences—and only secondarily to consider its effects on the range of psychosomatic functioning investigated in the over-all study. Neither the methods nor the findings of a number of variables will be discussed. Certain aspects of the emotional ratings, perceptual performance on a test involving area comparison, and the plasma level of hydrocortisone as an index of adrenocortical functioning will be considered. For ease of presentation, details of experimental procedure for these measures will be described in later sections, along with the data yielded by them. Elsewhere will appear a more detailed report of the biochemical findings.[18]

Experimental Stress Condition.—The stress condition consisted of two distinct tasks. *Length Estimation*, repeated on each of the three experimental days; and *Picture Description*, administered only on the third of these days. In both tasks the subject judged some visual materials, which in later validation against more detailed examination of the material proved to be partly or wholly incorrect.

Length Estimation: The subject was shown 15 pairs of lines, each pair ruled vertically, 4 in. apart, on white cardboard. The lines varied in length from 4¾ to 5¾ in. The minimum difference between lines was ¼ in.; the maximum, ¾ in. The subject had simply to tell which line of the pair was longer. Although the discrimination required careful viewing, the differences between paired lines were sufficiently large that virtually no errors were made in preliminary tests.

With his eyes fixed in an eyepiece, the subject could see nothing other than the stimuli uniformly illuminated at the other end of a viewing box approximately 2 ft. long. When the field was illuminated, a stop clock was simultaneously started, which was stopped when the subject responded. After each judgment the card was removed from the holder and laid before the subject, who, with a ruler, measured the two lines and declared whether he was right or wrong. In its essentials, the situation consists of two modes of making the same perceptual judgment—visual estimation and measurement—the latter conceived as validation for the former. Unknown to the subject, a number of cards were switched, so that the lines measured were different from those previously seen. The alternate lines were drawn so as to minimize any secondary cues by which the subject could discover the deception. On the first experimental day, the subject was led to fail in 6 of the 15 judgments; the following day this was increased to 8, and on the third, and last, day of the experiment, to 10, of the 15 stimuli. The order of paired stimuli was varied from day to day. Thus, the subject was confronted with the unaccountable experience of error in a rather simple perceptual judgment, since the stimulus differences, though small, were distinctly discriminable and the initial judgment was usually made with considerable confidence. Throughout the test, the experimenter's behavior reflected interested concern, perhaps some bewilderment that the patient was not readily able to judge the lines correctly.

Prior to the first day's session, the following statement was made, in essence, and repeated in part on subsequent days. It is reproduced in detail to give some picture of the implied meaning of the task.

"Every psychologically healthy person has to be able to make accurate decisions about what goes on in the world about him, both about things and

about the actions of people. As you know, mentally ill people are undependable or inaccurate in what they see or hear or in the judgments they make about things going on about them. Sometimes they see or hear things which are not there. We believe that the difference between psychologically healthy and unhealthy persons can be seen even in relatively simple perceptual judgments. In the test we will give you now, we want to see how accurately you can judge the size of lines. Although judging length is not very important in your daily life, we have found that being able to do this test is definitely related to the ability to make important decisions.

"I am going to show you pairs of lines, one on the right and one on the left. One line will always be longer than the other. I would like you to tell me which line is longer. Just give the position of the longer line—right or left. Before each pair of lines is presented, you will see a small cross, which will be shown again after you judge the lines. I would like you to keep your eyes on this cross until you see the lines and then continue looking at it after the lines disappear, until I tell you to take your eyes from the eyepiece. This is necessary to keep your eyes in the place where the lines are shown. After you make your judgment, the card will be taken from the viewing box, and you will have a chance to look at it closely and measure the lines to see whether you are correct or incorrect. Call out your measurements to the nearest quarter of an inch on this ruler, and tell us whether you were correct in your first judgment. Measuring the lines will give you a chance to know how well you are doing and to improve on later judgments."

From this statement it is clear that the subject was led to interpret the situation as a test of mental health, and inaccuracy as a sign of psychological breakdown. However, it should be pointed out again that the experimenter remained an essentially neutral figure, neither supporting this interpretation through further action nor showing disapproval of the patient for failure, or yet, at the other extreme, making any intentional efforts to allay the patient's fears. The experience of distortion stems primarily from the patient's relationship to the stimulus field, depending on the disparity between the original and the validational judgments, rather than on the transaction with the experimenter.

Picture Description: Following *Length Estimation* on the third experimental day, an additional procedure, intended to intensify the subject's experience of perceptual distortion, was administered. The subject was told that he had done poorly, more so each day, in judging length and that now another test was to be given bearing on his ability to make accurate judgments. However, it was explained, this procedure was felt to have greater importance than the previous test, since the material to be viewed was to be scenes depicting actual social behavior and, to our minds, was more closely related to the subject's ability to make judgments in life situations of social importance.

Using the same viewing apparatus, a series of photographs was shown briefly (0.25 second). The general procedure paralleled the *Length Estimation* task as closely as the difference in stimulus materials permitted. First, a picture was shown and the subject was asked to describe the scene; then it was taken from the viewing box and placed before him for more detailed inspection to check the accuracy of his report on the briefer viewing. As before, alternate plates were actually shown on the second occasion. In posing the pictures, the stimulus properties—number and positions of figures, details of clothing, lighting, and so on—were altered as little as possible.* Thus, the first picture shown was a man sitting, looking somewhat depressed, with a gun to his temple. The alternate version showed the same person in the same posture, though apparently in thought, now holding a pipe in his hand with the stem in about the same position as the gun barrel was formerly. The first picture is usually described as a depressed person attempting suicide; the alternate picture denies the self-destructive content entirely. Figure 1 shows this pair and one other used in this study. The more "threatening" version was presented tachistoscopically, and the more neutral alternate, for longer inspection immediately afterward.

Eight pairs of pictures were used†:

* Staff members served as models. Faces are shown only for those with whom the patients were not likely to have contact, either as part of the experiment or in the hospital generally.

† In some cases one or more of the pairs was not shown, when it seemed that the subject was becoming suspicious of the task or that we were "overdoing it." Similarly, in a few instances the first picture of the pair was shown twice if the subject's report denied the threatening content, in effect described the neutral version. Since the purpose of the task was to set up a convincing demonstration of perceptual distortion, both of these deviations from a fixed procedure seemed justified. However, they were used only occasionally. It should be noted that we were concerned mainly in the present study with the instrumental value of this technique in changing affective levels and in studying change in other variables. In a more extended study of the technique itself, the order neutral-threatening and neutral-neutral should be investigated.

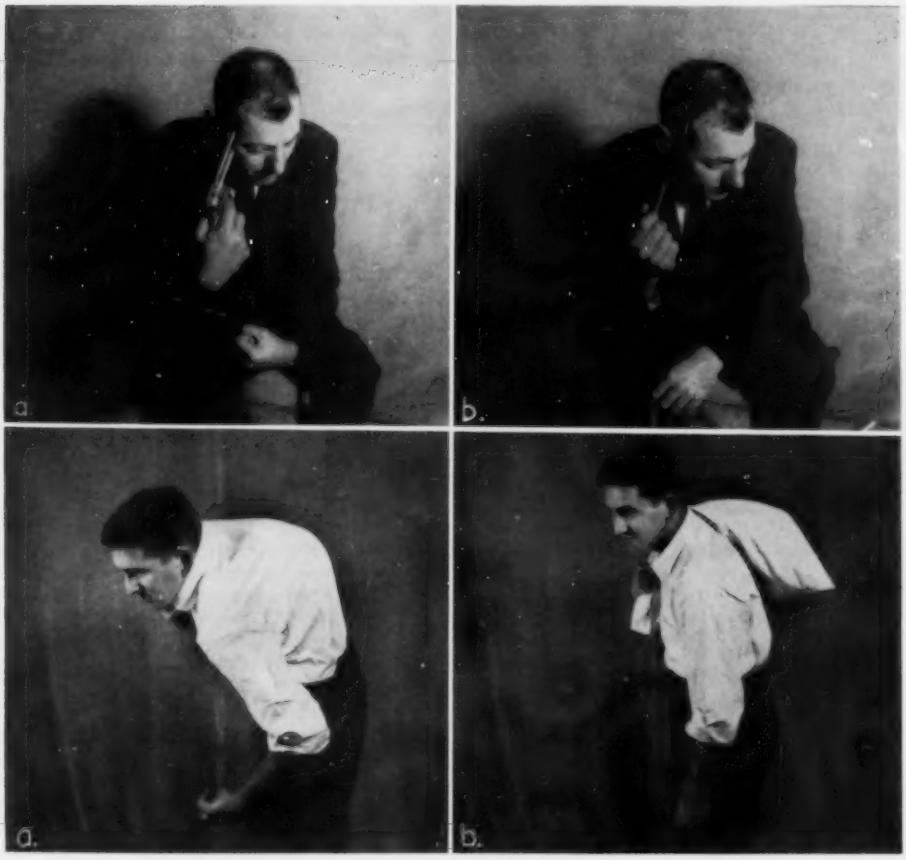

Fig. 1.—Two pairs of pictures used in the Picture Distortion procedure. The *A* version is rapidly exposed; the *B* version is then shown for more lengthy examination.

1.	A. Man with gun	B. Man with pipe
2.	A. Nurse pulling sheet over man's head as in death	B. Smiling nurse "tucking in" smiling patient
3.	A. Man with hands to woman's throat, as if throttling her	B. Man with arms in same position, but cupping woman's chin as if to kiss her
4.	A. Man and woman in embrace	B. Same couple in discussion
5.	A. Man dancing with man	B. Man dancing with woman
6.	A. Two men restraining or struggling with enraged man	B. Same men supporting an apparently ill man
7.	A. Tense, unhappy man bent over, apparently a hunchback	B. Same person, standing erect and relaxed, with laundry bag over shoulder
8.	A. "Boss" pointing, apparently in anger, to man across desk	B. Same "boss" extending arm for handshake

Although similar to *Length Estimation* in the effort to create the experience of perceptual distortion, this procedure adds the important suggestion that the distortion results from the projective intrusion of needs commonly denied consciously: self-destruction, sexual hostility, homosexuality, and the like. Consequently, the "errors" are hardly as innocent as misjudging which of two lines is longer; although both imply failure of ego function, the demonstration is decidedly more vivid

and, we anticipated, anxiety-provoking with the picture material.

Subjects.—Two groups—11 psychiatric patients and 5 normal young men—served as subjects in the four-day multivariate experiment, using the perceptual distortion procedure as a focal stress on the three experimental days. The psychiatric group was drawn from the inpatient population of the Institute for Psychosomatic and Psychiatric Research and Training of the Michael Reese Hospital, and were selected so as to be roughly comparable to an earlier group of patients tested in the same basic experiment but with an anxiety-provoking interview as the experimental stress. All of these patients were considered to be anxiety-prone on the basis of preexperimental interviewing and review of their clinical records. For obvious reasons, grossly disturbed patients could not be used, nor were any patently psychotic patients included. The present patient group consisted of seven men and four women, with a mean age of 39.8 years. The control subjects were U. S. Army enlisted men (mean age=22.4) recruited from the headquarters personnel of the Fifth Army Headquarters. A larger group was screened, and those felt to be most "clinically normal" were requested to participate in the experiment.

Prior to the experimental week, subjects were told only in general terms that they were to be given some physiological and psychological tests on a number (unspecified) of days. Afterward, subjects were interviewed, partly to get further information about their reactions to the various procedures, and largely to reassure them about the stress situation.

Results

Behavior on the Perceptual Distortion Tasks.—In the main, subjects accepted the procedures without protest and did not question, at least overtly, the intent of the tests. The general reaction to the recurring failure during *Length Estimation* was surprise, often chagrin, sometimes self-depreciating anger. Rarely was any suspicion of the examiner expressed, not even in later interviews with another investigator; nor did any fully developed conviction of being tricked appear. The often-made statement, "Something must be wrong," usually reflected genuine confusion, rather than the subject's suspicion of having been misused. Most subjects measured the lines scrupulously, though sometimes with the annoyed comment: "I can see it now; there's no point in measuring them to know I was wrong."

During the first day's session subjects expressed surprise at how far off they were in a particular judgment, but there did not seem to be any genuine experience of failure until they were told at the end of the session that only 9 of the 15 judgments had been correct. Still, the session often ended on a note of hope, as the examiner said that the performance had not been good but that he would try the task again the following day. Typically, testing on the second and third day was in a grimer atmosphere, with the subject determined to do better and more visibly perturbed by each "error." In a coming section, the emotional changes will be discussed further in terms of the ratings of affected response made by observers.

The subjects made considerable effort to understand why they were doing so poorly. A variety of hypotheses—ranging from bald rationalizations to quite elegant perceptual theories—were evolved in the effort to make meaningful the obvious failure, without, at the same time, ascribing it to personal inadequacy. Systems for estimating lines—e. g., using the distance from top and bottom of cards, rather than the length from end to end of the line—were tried and discarded. The brightness of the lights, thickness of lines, and other aspects of the displays served as explanations for error. During *Picture Description* the speed of presentation served as a further explanation for distortion. Many patients attempted to anchor their performance in terms of some "group norms"—"Am I doing as well as most people?"

Despite misleading feed-back, most of the line pairs were actually correctly judged on each of the three days. The poorest performing subject made 3 errors on one day, but over-all the mean number correct for the entire group on all days was 14.4 out of the maximum 15. Nor did this value change at all from day to day. The means

on the three days separately were 14.4, 14.3, and 14.5. Thus, despite incorrect information and the intended intensification of failure feelings, subjects were *in fact* no less correct on the last than on the first day. Similarly, decision time showed no regular or significant change across the three experimental days. If anything, the mean decision time on the third day was somewhat lower than on the first and second days. Subjects did, however, become more variable in the speed of judgments on successive occasions. There was some tendency to slow response on the judgment following one declared wrong, and consequently the day with the greatest number of errors had the greatest variability. Overall, however, the experience of failure had little effect on the quality of performance in the test task itself, other than to increase variability of decision time.

With the *Picture Description* task the initial descriptions were usually quite accurate and detailed. Although some patients stayed fairly close to the stimulus materials and gave rather literal descriptions ("Man with a gun to his head"), most volunteered some interpretation ("A man with a gun to his head about to commit suicide"). When shown the alternate plates, most subjects immediately saw the discrepancies, particularly when they had committed themselves to a psychological interpretation of the pictured events. However, in a number of cases the initial description was sufficiently vague that the alternate seemed to differ only in slight ways. Thus, the subject who said, "A nurse covering a patient," and not mentioning death, might simply comment, when shown the alternate version, that he had neglected to note that the nurse and patient were actually smiling. Most frequently, however, there seemed to be a genuine experience of misperception or misinterpretation.

As the series progressed, there was a tendency for some subjects' descriptions to become briefer, reporting only the most obvious aspects of the pictures, or to become more concerned with psychologically trivial details of the pictures. The subject, accused as it were of being inaccurate, became, instead, vague or compulsively detailed. It is difficult, from the material at hand, to tell whether the subject was simply suppressing report, or was in fact perceptually blocking, although it is our impression that there were genuine instances of a true reduction in the perception of the threatening material. Although we have too little information to justify any more extended discussion, it does seem that this task evoked defensive maneuvers, similar in kind to those described in experiments on "perceptual defense" and commonly found in the clinical use of the Rorschach test and other projective procedures.

Affective Reactions to the Perceptual Distortion Stress.—Throughout each of the four days of the experiment, two observers viewed the subject through a one-way screen and kept continuous records of behavior. Once during the early morning (*pre* period) and once after the stress (*post* period) the subject was interviewed for perhaps 15 minutes with the primary purpose of exploring changes in the extent and variety of emotional reactions in the experimental situations. From the observation and interview records, ratings were made for each of three discrete sections of each day: the period *before, during,* and *after* the experimental stress. The technique and reliability of these ratings have been discussed elsewhere and need not be considered here.[8] In brief, anxiety, anger, and depression were rated separately, each on a seven-point scale. Zero was taken to represent lack of the affect, and 6 as the greatest possible quantity. Along such a scale, most patients who could cooperate in this study tended to be at the lower end. In order to indicate the rather smaller amounts of change from occasion to occasion, "plus" and "minus" qualification was allowed, thus in effect

creating a 19-point scale. The mean values presented here are based on the conversion of these ratings to fractional numbers; elsewhere integer values have been used.[8]

Although originally focused on the experience of anxiety, early in this series of experiments it became clear that two other affective experiences, anger and depression, can readily arise in response to stresses of the type used. The combination of the three rated affects thus yields a gross index of over-all emotional disturbance in the experiment. In the present analysis this "combined affective rating" is taken simply as the sum of the three individual ratings.

Table 1 contains the mean affect ratings for each occasion for three experimental groups, the patient and normal subjects tested with the perceptual distortion stress and, for comparison, patients of the earlier stress-interview experiment. The three groups allow two important comparisons: the effects of different stresses on persons of roughly the same sort (psychiatric inpatients prone to anxiety), and the effects of the same stress (perceptual distortion) on persons quite definitely differing in anxiety and mental health generally (patients *vs.* normal soldiers).

It is clear, even on cursory viewing of the mean ratings in Table 1, that the perceptual distortion stress had the over-all effect of inducing emotional disturbance in both the patient and the normal subjects of the present experiment. Although there is a clear and significant difference in affect levels between the normals and either patient group, the experimental changes are roughly of the same order.

Except for the anxiety ratings of the patients' first experimental day, there is a general rise from the *pre-* period to the *during*-stress period in each of the ratings on each day. Since, as we have already noted, the impact of the first day's stress is not fully felt until the end of the test period, it is understandable that the ratings which represent the entirety of this period should not yet be elevated.

Affect levels stay up or, more usually, continue to rise in the *post*-stress period. For the patient group, this is least true on the third experimental day, when the response during the stress period was higher than in any preceding period. The normal subjects have a somewhat greater tendency to continue increasing after the stress period proper is over. Both normals and patients have their highest levels and largest changes from *pre-* to *during-* and *post*-stress periods on the third experimental day. However, only the normal group shows the anticipated increase in affective response from the first to the second to the third experimental day, paralleling the increase in the amount and variety of perceptual failure built into the experimental task.

TABLE 1.—*Levels of Affect Before, During, and After Two Experimental Stresses*

Affect	Group *	Pre Day	Day 1			Day 2			Day 3		
			Pre	Dur.	Post	Pre	Dur.	Post	Pre	Dur.	Post
Anxiety	Patient, interview	1.38	0.97	1.36	1.05	0.63	1.28	1.39	0.78	1.48	1.53
	Patient, perceptual	1.31	1.52	1.49	1.79	1.05	1.27	1.32	1.30	1.86	1.84
	Normal, perceptual	0.74	0.44	0.68	0.72	0.80	0.88	0.82	0.52	1.08	1.14
Anger	Patient, interview	0.55	0.72	1.04	1.02	0.61	1.41	1.29	0.77	1.35	1.06
	Patient, perceptual	0.86	0.93	1.14	1.56	0.83	1.02	1.13	1.31	1.69	1.59
	Normal, perceptual	0.12	0.00	0.12	0.18	0.12	0.40	0.74	0.06	0.40	0.46
Depression	Patient, interview	0.68	0.82	1.32	1.16	0.52	1.24	1.60	0.71	1.17	1.52
	Patient, perceptual	1.00	1.04	1.13	1.70	0.74	1.00	1.33	1.19	1.66	1.79
	Normal, perceptual	0.12	0.06	0.20	0.54	0.26	0.54	0.86	0.46	0.66	0.98
Combined †	Patient, interview	2.61	2.51	3.74	3.23	1.76	3.93	4.28	2.26	4.00	4.12
	Patient, perceptual	3.17	3.49	3.76	5.05	2.62	3.29	3.78	3.80	5.21	5.22
	Normal, perceptual	0.98	0.50	1.00	1.44	1.18	1.82	2.44	1.04	2.14	2.58

* The three groups include all subjects who completed the four days of the experiment and were rated in each period. For the patient group given the interview stress, N=18; for the patients given perceptual distortion stress, N=10; and for normals, N=5.
† The sum of anxiety, anger, and depression ratings.

Lastly, we may question whether the stress conditions, or the subject groups, differ in the pattern of affects aroused. Although both procedures were intended to produce anxiety, it is conceivable that the interview, which depends on the relationship of two persons, might be more likely to evoke anger than the more impersonal perceptual stress, in which the examiner is a less accessible or appropriate object. Again, it is clear in Table 1 that the changes in the three rated affects are roughly coordinate, indicating perhaps a general state of emotional disturbance rather than any more specified response. Hence, any indication of specificity would have to be in terms of rather small proportionate differences. If the levels during and following the stress are compared with the pre-stress levels, it does seem that the interviews produced proportionately more anger and proportionately less anxiety than the perceptual distortion stress. However, it should be cautioned that these differences are small and separate analyses have shown that the three affect ratings are actually highly related.

Effect of the Stress on a Perceptual Discrimination Task.—Another measure made on the preexperimental day, and before and after the stress of each experimental day, required the subject to discriminate squares varying in area. The present procedure is a somewhat modified and enlarged version of the Area Judgment Test used in the interview-stress study, and described fully in an earlier paper.[9] In its present form, the test had two major portions: 1. A series of pairs of squares (white on a black background) viewed simultaneously. The subject was asked to judge which of the two was larger. 2. A series of displays consisting of a square in the center, circled by seven other squares, varying in size. The subject's task was to identify the one among the comparison figures which exactly matched the central one in size. Although relative size is judged in both cases, the paired-stimuli version involve instantaneous viewing and allowed only a completely correct or incorrect judgment. Consequently, the second (multiple-stimuli) task was introduced to tap more complicated perceptual behavior, since the subject had to search the number of comparison figures, match, as it were, the standard to each, and decide which among the various possibilities came closest to the best match. When incorrect, the error made could represent greater or less deviation from the standard, and hence more sensitive scoring of the accuracy of performance was possible. The paired-stimuli series (48 items) and the multiple-stimuli series (14 items) were administered in succession on each *pre* and *post* occasion. Both versions were scored for *accuracy*, *decision time* (time from the exposure of the display to the subject's response), and *confidence*. (For each item the subject rated the certainty of his estimation, where 0% was a complete lack of assurance and 100% absolute confidence.)

Though performance on the two procedures differs in some particulars, in both groups the mean scores show substantially the same trends from period to period in regard to the three test dimensions of accuracy, decision time, and confidence of judgment. Consequently, for present purposes we can consider the two procedures as a single index of perceptual functioning in this situation. For convenience, the more easily described data of the paired-stimuli version will be discussed in the remainder of this section.

Since the stress was designed to produce an experience of perceptual failure, it was readily assumed that a test procedure similar in structure to the stress task (both involving materials presented for visual examination, discrimination, and judgment) would likely show the effects of the experimental intervention. Indeed, the original intent of this series of experiments[6] was to influence the action of biologically distinct levels of function by the introduction of stressers conceptually ap-

TABLE 2.—*Area Judgment Test (Paired Stimuli) Performance Before and After a Perceptual Distortion Stress for Patient (N=11) and Normal (N=5) Group*

Test Variable	Group	Preexper. Day	Day 1		Day 2		Day 3	
			Pre	Post	Pre	Post	Pre	Post
Accuracy, No. correct	Patient	29.0	32.9	31.7	32.4	32.7	32.4	31.5
	Normal	29.8	32.8	33.4	36.4	34.8	36.4	36.0
Decision time, sec.	Patient	4.18	3.93	3.89	3.93	4.29	3.83	3.98
	Normal	2.84	3.07	3.36	3.04	3.45	3.41	4.06
Confidence, ratings %	Patient	72.9	64.7	55.0	56.5	50.5	51.6	44.4
	Normal	59.2	60.8	62.0	64.4	65.8	66.4	68.0

propriate to each. Thus, the present experiment was expected to modify, perhaps first, perceptual functioning in the test situation.

This expectation is met in only limited degree. Table 2 gives the mean accuracy, decision time, and confidence values for the paired-stimuli Area Judgment test for the patient and normal groups of subjects on each occasion of testing. For each group there are only small, and insignificant, changes in the accuracy scores from occasion to occasion. Though the patients and normals start with virtually identical values, there is some indication of a greater degree of improvement over the three days in the normal group. However, the changes are small, and there is no direct evidence of stress-induced effects in this aspect of perceptual judgment. By contrast, the speed and confidence of judgment show more systematic effects, in the first case being similar for the two groups, and in the second case operating in opposed directions.

Although the differences are small and insignificant, there is a general slowing of response from the *pre* to the *post* measure, with the single exception of the patients on the first experimental day. (It is to be recalled that this was also the only occasion which showed no increase in anxiety.) In general the normals respond more rapidly than the patients, with the greatest, though not statistically significant, difference on the first day of the study (preexperimental day), when the patients had a mean decision time of 4.18 seconds and the normals one of 2.84 seconds. This is, of course, the subjects' first experience in the strange and somewhat forbidding laboratory, and it seems to be a general quality of the anxious person that he is less able to deal with, and consequently more uncomfortable with, any novel situation which requires unaccustomed behaviors. However, over the entire experiment the normal subjects tended to become slower on each successive occasion, whereas the patients stayed at roughly the same values, except for the small *pre-post* changes. An analysis of variance for the difference between the groups in the slopes of these curves yields an *F*-ratio short of significance. However, the decision time data of the multiple-stimuli task do show significant differences in trend between the two groups ($P<0.05$).

The greatest differences between occasions and between groups appear in the ratings of confidence. Although the rating system is quite arbitrary, and it is altogether conceivable that subjects use different internal frames of reference, the changes between successive test occasions for the same subjects can be interpreted as reflecting changes in the subjects' assurance while making these perceptual judgments. The patient group moves steadily from a higher to a lower level of confidence as the experiment proceeds (Table 2; Fig. 2). From their first-occasion high of 72.9%, the values go down occasion by occasion to a final mean of 44.4%. By contrast, the normal subjects move in precisely the opposite direction, although the over-all excursion is not as great. Starting with a mean level of 59.2%, they move steadily upward, reaching finally a level of 68.0%. On analysis of variance for trend, these two series

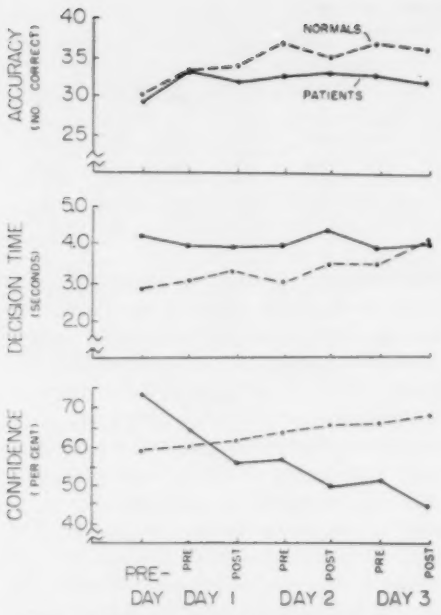

Fig. 2.—Mean Area Judgment test (paired stimuli) scores on each testing occasion for the normal and patient subjects in the Perceptual Distortion experiment.

are found to be significantly different ($F=4.46$; df, 6 and 89; $P<0.001$). The same analysis of the confidence values on the multiple-stimuli task yields similar significance, though at the $P<0.01$ level of confidence. There is, thus, a cumulative effect over the four days, though operating in opposed directions in the two groups. The patients become increasingly less self-assured in the face of the repeated perceptual failure experiences, whereas the normals, starting more cautiously, gain confidence as the experiment continues. The rising confidence of the normals perhaps realistically parallels their increased accuracy of judgment and may reflect an over-all adaptation to the experiment superior to the patients.

Effect of Stress on Adrenal Cortical Function (Plasma and Urinary Excretion of Hydrocortisone).—In an earlier paper [11] it was reported that the stress interview raised the plasma level of the adrenocortical hormone hydrocortisone, and that hormonal change was roughly proportional to the increase in emotional disturbance.[12] Complete and detailed findings of the hormonal effects of the present stress on the patient and normal groups of this experiment is being prepared for separate report.[13]

Suffice it to note in the present context that the level of hydrocortisone, and the stress-induced response, are roughly comparable in the patient group given the perceptual distortion stress and the earlier patient group, stressed through a psychiatric-interview procedure. The present group of normals shows a significantly lower level of adrenocortical function (both plasma and urinary output) on each test occasion than either of these patient groups. However, the relative stress response (*pre* to *post* change) was *greater* in the normals than in the patients on each experimental day (significantly so; $P<0.05$, on the second experimental day, and falling just short of this level on Day 3). Compared with their measures on the experimental days, the patients had proportionately more response on the preexperimental day than did the normal subjects.

In brief, by this index of hormonal activity, as well as the emotional and perceptual behavior just described, the perceptual-distortion procedure evoked substantially the same degree of change in anxious persons as the earlier interview stress, with proportionally more response shown by the normal subjects.

Comment

In a number of respects the perceptual distortion procedure is similar to the situation used by Asch [1] for the study of independence and conformity, which, in fact, contributed to the origination of the present method. In Asch's experiment a number of subjects are asked to view a stimulus line, and three comparison lines, and each is to say in turn which of the

comparison lines is equal in length to the standard. However, all but one of the judging group have in fact agreed with the experimenter to give previously decided incorrect comparisons on a number of occasions. Thus, as Asch characterizes the situation, the critical subject is submitted to contradictory and irreconcilable forces. On the one hand, there is evidence of a clearly perceived relationship between the lines, and, against this, is the unanimous agreement of a group of peers. Both these forces are in the immediate situation. Being obliged to state his judgment publicly, along with all the other subjects, the critical subject must take a public stand against the group. The situation, Asch notes, is self-contained: The critical subject can neither avoid nor evade the conflict by referring to conditions outside the experiment.

In the present experiment these basic conditions hold, except that the conflict—the "contradictory and irreconcilable forces"—is wholly within the subject's experience. The two competing definitions of what is true are both intrinsic to the subject's experience, one being represented in an initial perceptual act, the second in the validating judgment, and, unlike Asch's experiments, not depending upon social consensus. As a consequence, the present situation does not allow the resolutions possible in Asch's experiment, indeed the phenomena which he was concerned to study, taking an independent stand despite the isolation from group agreement or renouncing of one's own judgment and conforming to the group standards. Consequently, the contradiction is more truly irreconcilable because the failure of agreement is located within the subject.

Nor is there any question from findings available that the experimental condition did lead to emotional and certain coordinate disturbances. For most subjects there seems to have been a similar sequence of events. The conflict was first reacted to with surprise, and, within the first session, no marked disturbance. Following this was a quest for explanation, an effort to understand the disparity between the original and the validating perceptions. Many of these explanations were sufficiently acceptable, at least to the subject, that the recognition of failure was delayed or avoided. More typically, however, the continued experience led to confusion, and with it affective arousal. A stage of defense minimized the amount of affect released. During *Picture Description* performance, one type of defensive maneuver consisted of reducing the amount of commitment by reporting less, or less important, material in the original account, which, therefore, implied less distortion when shown the second version of the picture. There were attempts also to minimize the importance of the entire test and to withdraw from the situation. Generally, however, subjects were left with the feeling of uncertainty and anxiety, which extended well beyond the period of testing into the remainder of the day. By the time of the final interview, they still showed concern about their inadequacy and its implied interpretation. Interestingly, in some cases, subjects reported compensatory activities, such as practicing estimating lengths in order to improve this ability.

Any situation which a subject perceives as threatening his integrity as a person is potentially stressful. Anxiety is aroused when danger is anticipated which can be neither avoided nor mastered and whose consequences are expected to be destructive, although usually the precise time, locus, or extent of the potential damage is not known. Whether any particular situation is stressful depends on the interplay of a number of distinguishable factors, some residing in the subject, others in the stimulus and the larger situation. We may schematize these factors, commenting on a few in terms of the present findings.

1. *The Subject's Needs, and Relevance of the Stress Agent to Frustration of These Needs.*—For stress to exist, some need state of the subject must be threatened. In

general, the more important the threatened need to biological survival or to the integrity of the personality, the more likely is the stimulus to evoke stress response. Conversely, the more peripheral the need attacked, or the less relevant the stress object to centrally important needs, the less likely is an intended stress agent to produce disturbances of behavior. In the present experiment, it was assumed that the need for cognitive orientation, to know a dependable external world, is a basic need, although, we may suppose, differing in importance and as it relates to other needs in particular personality organizations.

Parenthetically, it should be noted that the perceptual distortion situation is similar in form to many failure-stress conditions that have been used in the psychological study of stress, although, we believe, differing importantly in intent. In the typical failure-stress, the subject is given some, usually intellectual, task which he can not satisfactorily complete or for which false scores are given. Often performance on the stress task is evaluated against some external norm, defined in terms of the behavior of positively or negatively valued reference groups. For example, subjects are told: "Other students average 72; your score is 50," or "WPA workers have completed most of these problems; you did less than half." In such cases, the frustration of needs for achievement, status, or recognition is assumed, and the effectiveness of the experimental situation depends on the degree to which the subject perceives failure in the test task as relevant to these needs. Clearly, the present situation is a failure-stress in this sense—making errors in line estimation or picture description shows inability in perceiving and judging, which the instructions imply most "mentally healthy" persons can do with greater facility. But, more importantly, it was expected that the task would constitute prima facie evidence of a more profound order of psychological malfunctioning, implying the inadequacy of ego control, of greater importance to most subjects than achievement or status.

2. *The Subject's Ego Strength and Defenses.*—The degree to which any stress may lead to behavioral disturbance depends on the subject's ability to maintain integrated functioning in the face of stress and has been expressed in such concepts as frustration tolerance, ego strength, or, stated conversely, affect proneness. All such concepts imply some characteristics of the personality organization involving thresholds beyond which stress stimulation leads to disturbed behavior. Though individual stress resistance can be characterized in general terms, the particular effects of a given stress depend on motivational and situational factors. Closely allied to these general thresholds of stress tolerance are the specific defenses available to the person for emergency use to prevent the development of disabling anxiety or other disruptive consequences of stress. Not only do persons differ in the defenses with which they encounter any new stress, but situations differ in the degree to which they allow particular defenses to operate. In this experiment, the situation was so constructed that certain defensive maneuvers were less possible than, for example, in the interview-stress situation studied earlier. Because of the less direct involvement of the examiner, the subject could neither use him as a target for hostile projection nor, as sometimes happened in the interview experiment, interpret his actions as therapeutic.

The patient and normal groups may be described as differing grossly in ego strength, if only on the basis of the history of their social adjustment. The obtained findings reflect in fair measure the differences in the stress behavior of persons differing in ego strength. But before interpreting these findings, we should consider a third set of factors important in the understanding of behavior in any stress situation.

3. *Relation Between the Stress Condition and the Larger Psychosocial Situation.*—

The impact of a particular stress depends not only on the nature of the stress and the personality structure of the individual, whether considered in terms of motivational or structural properties, but as well on the larger context. The stress takes place against a background of other continuing events, which may define, in the first place, the meaning of the particular stress and, second, the magnitude and types of response. Bettleheim [3] noted that arrival at the Nazi concentration camp was often accompanied by feelings of relief, since it meant the end of a harsh and dangerous trip, although the arrival considered alone was the beginning of a much longer and almost equally stressful period. We are simply calling attention to a general proposition described in many more specific and detailed ways in psychological research on anchoring, frame of reference, or adaptation level. The response to a stress stimulus, as to any stimulus, depends on the surrounding stimulus conditions and earlier behavior of the subject.

With these considerations, we should like to suggest an interpretation of the various experimental findings in terms of the differences between subject groups and as a function of the psychosocial context.

As part of their chronic anxiety state and lower ego strength, we might assume that the patients anticipated and entered the experimental situation with a higher level of anxiety than did the normals. Moreover, they were generally more disturbed by the situation as a whole. For them, participation in the experiment was a much more serious matter, since they might easily assume that the information gathered might bear on the length of their hospital stay or prognosis generally. By contrast, the normal soldier volunteers knew only that some tests were to be given, which bore little or no relation to their life outside the experiment. Since participation meant release from four days of duty, it might even have been anticipated with some pleasure. Consequently, the patients and the normals are found to differ in the most general indices of psychosomatic disturbance—in this study, affect levels and the measures of plasma hydrocortisone and excretion of urinary hydrocorticoids—both initially and throughout the experiment.

In terms of such nonspecific indicators, the first day in the laboratory was most disturbing to the anxious patients, and distinctly less so for the normals. In the present study this is seen in the proportionately greater adrenocortical response on the preexperimental day; with the earlier interview-stress patient group significantly higher affect levels were found as well.[15] For the anxious patient the novel situation, with its unknown dangers, coupled with the realistically frightening look of the laboratory, with its complex equipment and professionally detached experimenters, constitutes the most real threat of the experiment. Against this, the intended stresses in both the interview and the perceptual distortion studies produce proportionately less additional response (again mainly in terms of the adrenocortical index). While both the normals and the patients show greater affective expression to each day's perceptual distortion stress session, it is only the normal subjects who show the anticipated adrenocortical response. These findings may be interpreted in at least one of two related ways: (*a*) As the initial level rises, a limit of response is approached, and an increasingly large increment of stress is necessary to produce further response; the specific stress of this or the interview experiment was not of this intensity. (*b*) The major source of disturbance was the unknown danger seen in the preexperimental-day response; thereafter there is a process of adaptation, against which the intended stresses were less potent. One might say that the subject having lived through the first day without catastrophe, later stress sessions could not produce further disturbance. In any case, the greater focal response of the normal subjects to the stress proper parallels their lessened sensitivity to the situation as a whole. Despite their over-all lower levels of affect, the before-stress to stress rises

were no smaller than the patients', which might, indeed, be interpreted as showing proportionately *more* response.

The Area Judgment Test may be considered the most specific of the dependent measures, since it is closest to the stress task both in structure and in the function assessed; and it is here that the most explicit differences are found of the sort which might be expected between subjects differing in ego strength. Neither group shows any appreciable pre- to post-stress change in the accuracy of the perceptual judgments, though there is some tendency for the normals to improve over the four days. For most subjects it can be assumed that making the discriminations accurately is to them the most important part of the test; although no "accuracy set" is explicitly given, the assumption that this is what leads to a "better" score is easy to make. Speed was not even mentioned; the clock and recording of time were out of view, and the self-rated confidence levels might seem like a secondary and subjective aspect of the task. The groups do not differ in the major test variable, accuracy, but do in those dimensions less likely to be considered as bearing on the adequacy of their performance—speed and confidence of judgment. Despite the anxiety aroused, both groups apparently are able to attend to and discriminate between the test stimuli about as well after as before the experimental stress. (For an account of the mechanisms believed involved, the discussion of similar findings in the earlier stress interview study[9] is referred to.) However, while the patients stay much the same, the normals become distinctly slower in arriving at their judgments, particularly so in the more complicated judgmental situation. Their response to the repeated failure of the perceptual stress is apparently to expend more time, perhaps to become more certain before announcing their decisions. Paralleling this trend, confidence ratings increase from occasion to occasion. Despite their general disturbance, confidence in *this* task increases, as indeed their performance improves. The continued fall of confidence in the anxious patient group would seem to be a carry-over from the stress situation and to reflect their lessened capacity to absorb this failure and retain their self-assurance, despite the fact that they were actually capable of maintaining their performance, as measured by the accuracy scores.

Summary

A technique was developed for use in an experimental study of stress behavior of anxious patients and normal subjects. The subject was led to believe that his perception was inaccurate or distorted by producing a discrepancy between an initial judgment and a later validating judgment, thus creating a conflict between two definitions of external events. Such conflict was expected to be emotionally disturbing, since it implied ego malfunctioning. The technique was used on three days, following a pre-experimental day without specific stress. In addition to describing behavior in the situation, we have presented some selected data—affective, perceptual, and endocrinological—measured before and after the stress to evaluate its effects.

The experimental stress was found to be convincing and to lead to discernible emotional response both in the patients and in the normals. The normal subjects' responses are more specific and appropriate to the focal stresses, and in general more adaptive, as revealed in the pattern of before-and-after measures. By contrast, the more disturbed patients are more responsive to the situation in general; their behavior is less related to the specific stress events. The experimental findings are discussed in terms of three dimensions of a stress experiment: (1) the subject's needs, and the relevance of the stress to their frustration; (2) the subject's ego strength and defenses, and (3) the psychological context of the experiment.

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Emotional Determinants of Mental Deficiency

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The inclusion of the topic "emotional determinants of mental deficiency" in this workshop is a recognition of both a practical diagnostic problem in the clinic and a theoretical issue of prime importance for the understanding of behavior. The first presents itself as the task of distinguishing between an emotional disturbance with secondary or complicating feeblemindedness and mental deficiency accompanied by symptoms of emotional maladjustment. The clinician feels an urgent responsibility for making this distinction, since formulations as to etiology, prognosis, and treatment differ markedly in the two instances. The second task, the theoretical one, is to determine whether, to what extent, and by what mechanism emotional disorder may temporarily or permanently impair intellectual faculties. A parallel question, subsidiary for our present deliberations, is the impact of intellectual deficit on emotional life. These topics are far too large to be treated comprehensively in the brief time allotted, even had I the knowledge. I propose only to bring to your attention some of the conceptual difficulties that beset clinical efforts in these areas.

Even the terms which we employ are undergoing change in the midst of our deliberations. The W. H. O. Joint Expert Committee [1] has suggested that we reserve "mental deficiency" to refer to biological adaptive inadequacy and employ "mental retardation" to refer to educational and social performance below inferred intellectual endowment. Thus, in the following discussion, mental retardation would more properly apply than mental deficiency, though I shall at least briefly consider whether "emotional determinants" can produce permanent limitation in intellectual function.

Moreover, it is necessary to clarify the sense in which the term feebleminded is being employed.[2] On the one hand, it is frequently used as an adjective to describe inferior intellectual performance as revealed by social and psychometric measures. In this sense, behavior is feebleminded or not, never "pseudo," unless we refer to cases in which a low test score is falsely reported. On the other hand, feeblemindedness is often used as a noun to designate a diagnostic *inference* about the capacity underlying the measured performance. Here, the term is reserved for disorders which, however great their diversity, have in common a reduced intellectual capacity, usually permanent in nature. With this usage, observed feebleminded behavior is "pseudo" if it is the consequence of a sensory, emotional, or educational disorder that is interfering with the display of normal native endowment. However we employ the term, it is well to keep in mind that feeblemindedness constitutes not a disease but a clinical phenomenon, which itself requires to be differentially diagnosed.[3]

When we turn to the task of distinguishing between mental defect and emotional disorder, it is necessary to reemphasize the distinction between symptoms and disease entities. The A. P. A. manual, for example, defines psychoses as "disorders characterized by a varying degree of personality disintegration and failure to test and evaluate correctly external reality. In addition, individuals with such disorders fail in their

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ability to relate themselves to other people and to their own work."[4] Does this not apply in some sense to every severely feebleminded person? Is not the idiot or imbecile unable to test and evaluate correctly external reality? Is his personality not poorly integrated and his relation to others and to work not defective? The behavior could, with full justice, be described as psychotic.[5] But is that equivalent to a *primary* diagnosis of psychosis?

The urgency of the distinction is all the greater when we recognize that the defective requires to be institutionalized, in most instances, less because of his slowness in learning per se than because of traits of behavior unacceptable to his family and community: tantrums, disrupting the classroom, bizarre mannerisms, asocial acts, and so on. The intellectual inadequacy, which of itself impairs the ability to adjust to the environment, provides at the same time greater burdens of adjustment. Thus, disordered emotional behavior is frequently an accompaniment of intellectual limitation in the mentally defective patient who comes to medical attention.

I am not at all arguing for the inclusion of the severely defective under the diagnostic rubric of psychosis. Such a view, it seems to me, would be gravely in error, for it would aggregate two already highly heterogeneous diagnostic categories.[6] I make the point because there is too widespread a tendency to argue from the presence of bizarre and manneristic behavior in the defective to a primary diagnosis of emotional disturbance, to which the intellectual inadequacy is said to be secondary. On the contrary, maladaptive behavior and disorganized emotional responsiveness seem to me the almost inescapable consequence of a restricted capacity to learn and to conceptualize relationships. Such symptoms are no more an evidence of a "functional" origin of the total disorder than are the psychotic symptoms displayed in other brain syndromes, which may mimic almost perfectly any of the functional disorders. With so marked a degree of brain dysfunction as to result in severe intellectual handicap, is it not to be expected that the neuroanatomical substrate for emotional integration will be defective? This is not to imply that the symptoms of emotional maladjustment may not require treatment, or that, if they are treated successfully, there may not ensue a marked enhancement of social function. I do mean that if we are to design effective therapeutic methods, we must begin with a recognition of the differences in pathogenesis.[7] We cannot legitimately reason from similar effects to identical causes.

On the other side of the coin, many psychotic children display feebleminded behavior. With major disruption in personality organization and human relations, testable intelligence and social maturity are likely to deviate markedly from developmental norms for age. Indeed, it is not uncommon for the psychotic child to be diagnosed as defective at some stage in his parents' Odyssey through medical clinics. At times, it is only amelioration of the psychiatric disturbance that will permit the display of entirely convincing evidence of good endowment. But this is the very nature of the challenge to the clinician: to discern the basic psychopathologic process beneath the melange of symptoms of disordered behavior. It is not our task here to outline a scheme for differential diagnosis. Let us admit that there will be cases in which differentiation is difficult, or even impossible; time or trial of treatment may be required. But an orientation toward an adequate conception of diagnostic categories and toward the importance of an accurate differential diagnosis is fundamental to all further research and treatment. It begins with the realization that isolated symptoms are not a disease.

This brief clinical prologue foreshadows the complexity of the fundamental theoretical problem we must next consider: the relation between "emotion" and "intelligence." As clinicians, we refer to pathologic deviations in these functions as though what con-

stitutes each function itself is self-evident. In fact, we lack a completely satisfactory definition of either. This is the more forcefully true in the case of "emotion." The physiological concomitants of feeling states, in which many still hope to find "objective" measures, simply fail to distinguish adequately between one emotion and another. Our judgments rest solely upon introspective and empathic knowledge, with all of the uncertainty this implies. The experimentalist will prefer to avoid the term altogether and to hew to "motivation," which he can circumscribe in terms of the variables he is able to manipulate. The clinician will infer emotion from the perceptual, autonomic, and cognitive operations he observes and will consider emotion as motivation. In the ensuing discussion, I shall refer to studies on both emotion and motivation as these affect intelligence, since the interplay between the two is highly relevant for our problem.

All too frequently, intelligence and emotion are treated as though they were independent faculties of mind. This temptation stems perhaps from the commonplace observation that at times we act upon what we "feel," even though it contradicts what we appear to "know." The conception that intelligence and emotion are in any way independent attributes of mind is fundamentally in error; to the contrary, they are interpenetrating abstractions from observed behavior. Any emotion involves cognitive activity at the very outset, for example, in the identification—or misidentification—of the significance of the external or internal stimuli to which the organism responds. Intelligent behavior is stimulated by, and in turn generates, emotional forces as motivating factors. Interplay in both directions is fundamental to each. Indeed, our inferences about emotional operations are drawn from deviations in perceptual and rational behavior. In this conceptual framework, it would seem inevitable that emotional dysfunction will be accompanied by retardation, and perhaps even by irretrievable deficit, in intelligence. Conversely, defective intelligence must have a profound influence on the course of emotional maturation.

Whatever global definition of intelligence we employ, ease of learning and skill in problem solving will occupy central positions. Experimental investigations have demonstrated that the acquisition of classical [8] and operant [9] conditioning is a function of the state of the organism at the time stimuli are presented. The relevant variables are usually identified by the deprivation of basic needs to produce states of enhanced responsiveness; in the human subject, these are associated with changes in feeling tone. The hungry, but not the sated, dog will salivate when food is displayed; the thirsty, but not the well-hydrated, pigeon can be induced to emit any previously selected item of behavior within his repertoire which the experimenter chooses to reward by a drop of water. The heightened state of central excitation facilitates the formation of connections between previously unrelated external and internal events. Brain self-stimulation experiments have carried this somewhat further in identifying central loci with "rewarding" and "punishing" qualities, as measured by the induction or avoidance of certain behavior.[10,11] In these situations, there is no prior "deprivation," as least so far as we know, but only anatomical readiness to respond in one or another fashion. The relevance of these phenomena to "emotional" behavior may be inferred from the persistence of lever pressing for brain "reward" during intervals in which the imminent arrival of painful peripheral shock has been signaled to the animal.[12] In other situations, such as lever pressing for food reward in the hungry animal, this "anxiety-laden" period of anticipation is accompanied by the cessation of ongoing purposive behavior. It is tempting to speculate that the electrical stimulation of what Olds terms the "pleasure systems" in some way alters the subjective experience of discomfort associated with the anticipation of pain. We now have documented

for us a whole new array [13,14] of internal motivations that influence learning; it is difficult to resist the inference that these systems are related to emotional functions by analogy to the "satisfactions" we associate with lessening of deprivation in parallel experiments on satiation of needs.

In like fashion, the patterns of behavior we define as problem solving will be elicited only under circumstances in which the "solution" has utility for the organism. In the animal, the drives we can manipulate are at least relatively simple: hunger, thirst, sex urge, etc. Whatever subjective experience accompanies them must forever remain unknown to us. In the human organism, motivations become more complex and difficult to analyze: needs for security, approval, status, etc. Whether we consider these motivations as ultimately derivative from simpler biological needs or as forces at a higher level of integration that spring into being through social evolution, they become prime movers in determining the avidity with which methods for solving problems will be sought—and hence in determining functional intelligence. Cross-cultural studies demonstrate conclusively that academic performance, one measure of intelligence, is significantly molded by ethnic and socioeconomic value systems. Moreover, there is reason to believe that these habitual modes of response to academic challenge become built into the individual and characterize his behavior as emphatically as though they were innate.

The specifically human characteristics of the child, which include those samples of behavior from which we infer intelligence, quantitatively and qualitatively different from that of our nearest evolutionary forebears, are *social products*. They presume a native capacity for forming interpersonal attachments, a capacity which is further developed and enhanced in the course of those relationships. Piaget's monumental studies on the comparative development of intellectual operations document their dependence upon social interactions, which lead gradually to the substitution of consensual for egocentric processes. But all of this presupposes a relationship with others such that what they say and do makes a significant difference to the child. A hypothetically isolated child would fail to show these transformations and would remain at an animistic, nonverbal level. If we suppose a distortion in the course of interpersonal relatedness, then the assimilation of other's views would be expected to proceed in a perverted direction. Intelligence would fail to develop with the speed and in the direction of which it might have been natively capable—if we may momentarily consider it as an isolated potentiality.

The most extreme form of this distortion may be seen in the severely autistic child.[15,16] Lacking, for whatever reason, the ability to relate to other persons, he shows marked deviations in the development of communication—from total absence of speech through highly idiosyncratic use of language. His behavior in the verbal area is defective. The question may be properly raised: What right do we have to infer that he has the endowment for normal intellectual development? It must be admitted that the evidence is at times only indirect. In part, it is based upon performance tests, whose correlation with other measures of intelligence is uncertain. In part, we judge from isolated evidences of highly organized and complex rituals, from behavior that demonstrates unusually detailed recollection of past events, and from the presence in other, but less severely autistic, children of unequivocal evidence of good native endowment.[17]

If we agree that intellectual potential was originally good, then we have in the autistic child a demonstration of profound effects on intellectual performance from disorders in the affective sphere. The lifelong pattern of "pseudofeebleminded" behavior in the unresponsive cases may reflect the persistence of the autistic process, which continues to obscure native capacity. In my

estimation, it is more likely to reflect a permanent degradation of intelligence as the result of its inability to grow through essential early stages. Evidence from psychobiological studies of central nervous system maturation indicates that there may be critical stages in development at which interaction with environmental stimuli is essential for the maintenance of the metabolic integrity of nervous tissues; if the necessary reinforcement for enzyme systems is lacking, the capacity for function and development may be lost permanently.[18-21]

Neurotic disorders provide no less convincing, if less extreme, evidences of decrement in intellectual performance. Experimental "neurosis" in animals is associated with diminished capacity for discriminating between stimuli and for new learning; the very traits we term neurotic are characterized by their maladaptive—that is, unintelligent—function for the goals of the organism.[22] Clinical experience provides examples too numerous to list in comprehensive fashion. The severely anxious patient fails to attend to significant cues from his environment and cannot mobilize his reservoir of knowledge for the solution of current problems. The obsessive patient, preoccupied with unessential details and compelled to complete each subassembly, loses sight of the larger goal; his disability is particularly apparent on time-limited tasks. The patient who is convinced of his own inadequacy becomes paralyzed in the face of an intellectual challenge that may be well within his theoretical abilities. A poor child-teacher relationship is associated with less efficient learning, and so on. From the severe intrinsic to the transient situational emotional disorder, we observe detectable effects on intellectual function.

When we ask by what mechanisms these interactions between emotional and intellectual functions occur, we enter an extremely significant, but relatively unexplored, area. The lack of investigations of this problem probably reflects the conceptual compartmentalization which has led to a sharp limitation of studies to one or the other aspect of behavior. Decrease in vigilance and constriction of the field of awareness[23] are associated with emotional perturbations. Moreover, the emotionally disturbed subject has characteristic dysfunctions in the process of generalization, both the failure to extrapolate from the concrete and the formation of spurious generalizations. At the biological level of integration, one might postulate that affective states have a nonspecific effect on the permeability of synapses, thus facilitating or impeding the establishment of connections. There is some evidence that the maintenance of attention is dependent upon brain-stem centers[24,25] that are at least potentially at the service of the effector apparatus of emotional expression. At the psychological level of integration, it is clear that intelligence is a hierarchical function. Earlier learning sets are the prerequisite for the acquisition of more complex intellectual performances.[26] There appears to be a factor of "learning to learn," which may be strongly influenced by motivational determinants.[27] Deficits at any one stage of development of intelligence thus have far-reaching consequences for subsequent performance.

When, as clinicians, we are faced with inferior intellectual performance on the part of a child in whom we infer the presence of good "native" ability, we frequently regard this as the result of a "block." The tacit assumption seems to be that intelligence is intact, but merely hindered in its display by emotional barriers. This formulation merits closer examination. May not the observed intellectual deviation be an integral part of the very psychopathologic process we are striving to understand? This seems to be the case in the schizophrenias, whose clinical stigmata are to be found in disorders of thinking.[28] I suspect that it is equally true for the neu-

roses but escapes our attention because the effects are less gross.

In similar fashion, emotional behavior is no less dependent upon intellectual function. It is the cognitive apprehension of the significance of external stimuli that calls into play the appropriate feeling tone. It is one's judgment of the menacing or welcoming nature of the situation in which he finds himself that determines whether he responds with fear or with pleasure. The thoroughness of our intellectual appraisal of the justification of a course of action will generate the conviction, the emotional strength, with which we pursue it. Emotional forces are commonly regarded as autonomous, instinctual in origin, and capable only of sublimation. To the contrary, emotional life is qualitatively altered through social interaction mediated by the developing intelligence. We deal, not with secondary and pallid derivatives of instinctual forces, but with genuinely new emotional phenomena at a higher level of integration.[29]

From this point of view, impairment of intellectual function will inevitably impede emotional responsiveness. The degree in given situations will depend upon the complexity of the intellectual activity required for the proper appraisal of particular patterns of social interaction. Thus, mental deficiency per se provides a limitation for emotional maturation, above and beyond the emotional consequences of social nonacceptance because of the retardation. This will be especially true in the lower ranges of intelligence. This conception implies that the psychopathology of behavior disorders in the defective will differ qualitatively from those in the nondefective; it carries as its corollary the need to evolve specific and different modes of treatment for these emotional aberrations.

Recent neurophysiological studies on the limbic brain and on the "diffuse" activating systems in brain stem and thalamus appear, at first glance, to offer an anatomical repository for "emotion," with "intelligence" delegated to cortex.[30-32] But these same studies give equally impressive evidence of the essential nature of the interconnections between these phylogenetically somewhat separate systems. Cortex is necessary for the normal function of these lower centers,[33-35] just as the lower centers provide the background of diffuse activation upon which specificity and selectivity are superimposed by cortex. If we do not misconstrue the data in the tempting search for loci of separate mental faculties in normal behavior, they do provide a neurophysiological model for disordered function when one or the other element in this interplay escapes the control of the other. Outbursts of sham emotion[36,37] may stem from autogenous activity in allocortical and subcortical centers in the brain-injured.[7] Spike discharges radiating out from scarred areas have been shown to interfere with the ordered electrical activity essential for acquiring conditioned learning.[38-40] Similarly, defects in the inhibitory and integrative control normally supplied by cortex may lead to impulsive behavior, driven by more primitive emotional effector systems.

The interdependence of emotion and intelligence is a fundamental fact of human behavior, at the psychological and the biological levels of integration. We should no longer wonder at the evidence of dysfunction in either in the presence of disorder in the other, but rather ask: By what mechanism has it occurred in the particular case, and by what means may it be remedied?

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Observations on Schizophrenic Patients After Iproniazid and Tryptophan

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The employment of drugs acting on the central nervous system has been predicated largely on an empirical basis, the anticholinesterase compounds serving as an exception. As our understanding of the chemical constituents and their function in brain broadens, one can begin to see that basic theoretical information will be the foundation for new therapeutic approaches in this field. The observation that the effect of reserpine may be mediated through its action on liberating serotonin,[2] the changes observed with diethylaminoethanol, an analogue of acetylcholine,[3] and the utilization of antimetabolites of serotonin,[4] all of which modify behavior, are a few examples of this theoretical approach.

It has been found that iproniazid is a potent monoamine oxidase inhibitor in vivo,[5] and since serotonin can be degraded by this enzyme, it is apparent that the mechanism of action of such a drug may result in an increase in cerebral serotonin, and this has, in fact, been demonstrated in animals.[6] Since it has also been shown that serotonin may be involved in nerve conduction,[7] an accretion of this compound in the brain may produce alterations in normal nervous function. Thus, other workers[8,9] have reported behavioral changes after iproniazid treatment. However, these changes were produced only after prolonged treatment, and such a procedure might be contraindicated, owing to the side-reactions the drug may produce.

It has been demonstrated that the immediate precursor of serotonin is 5-hydroxytryptophan (5-HT), which can pass through the "blood-brain" barrier.[10] This compound has many undesirable side-effects, but the dietary precursor of serotonin, L-tryptophan, which can be converted to 5-HT, does not have these deleterious properties in physiological amounts. Thus it was thought that if the degradation of serotonin could be impeded by a monoamine oxidase inhibitor, and its synthesis simultaneously accelerated by giving the precursor from which it is formed, effects might be obtained which were more pronounced.

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This procedure is further justified by our lack of knowledge concerning what margin of safety exists in the monoamine oxidase system, and what are the normal physiological limits of brain serotonin levels. This technique therefore makes monoamine oxidase more of a limiting factor than that achieved with the inhibitor alone.

Methods

A. General Organization of the Experiment

A group of seven male patients with a diagnosis of chronic schizophrenia constituted our experimental group. In addition, some metabolic measurements were carried out with 17 male volunteers of similar age and with another group of 26 male schizophrenic patients.

After 12 days, during which the battery of psychological, psychiatric, and chemical tests were administered (pretreatment period), the patients received daily doses of iproniazid and tryptophan for six weeks. In the course of this treatment period the biochemical observations were gathered once a week. At the end of the fifth week the psychological and psychiatric tests were repeated.

The patients were maintained on closed wards (total number per ward, 52 patients) of an acute intensive-treatment center. In this setting all patients were exposed to daily exercise programs, including swimming, soft ball, basketball, and general gymnasium activities. They also spent time daily in occupational therapy and participated three times weekly in recreational therapy, which included listening to phonograph records, playing musical instruments of their choice, refreshments, and card games. An experienced staff of 12 to 14 nurses, aides, and student nurses kept the patients constantly occupied. No change from this routine took place while our seven patients went through the treatment period.

B. Food and Drugs

To this group, as to all other patients, considerable liberty was given in choosing the composition and quantity of their food, so that the diet came close to the self-selective type. If necessary, the dietitians enriched the selection with additional items as an attempt to ensure balanced nutrition. The actual consumption was recorded, and from these data the protein and tryptophan[11] intake was calculated.

L-Tryptophan (molecular weight, 204.22) was given in daily doses of 0.1 mM/kg. In order to cover the unpleasant, bitter taste of L-tryptophan, this amino acid was suspended in fruit juice (apple, grape, orange) with the help of the Waring Blendor. Apricot juice plus egg white was particularly well tolerated. On two occasions, one patient refused to take the suspension and had to be fed by tube.

The patients received daily doses of 7μM/kg. of iproniazid phosphate (molecular weight, 277.22) in the form of tablets. The doses were adjusted to the next smallest half-tablet (25 mg.). In only one patient a side-reaction, in the form of a mild case of postural hypotension, occurred after three weeks of treatment and disappeared after a few days without interruption of the drug administration. This amount of iproniazid is smaller than that used in animals for blocking monoamine oxidase in vivo,[12–15] but large enough to produce marked inhibition of this enzyme, assuming that the drug is uniformly distributed over the body.

C. Description of Patients

The seven patients, who from here on will be referred to by the designations A through G, respectively, were chosen because of the severity and chronicity of their illness. The duration of their overt psychotic periods extended from 2 to 12 years. All had previous hospitalization and treatment, including chemotherapy, electric convulsive therapy, insulin coma therapy, and individual and/or group psychotherapy. Three and four courses of ECT and ICT had previously been given to several of these patients.

The longitudinal history revealed that Patient E, who had been overtly psychotic for over two years, also had an extremely poor premorbid adjustment. He was 26 years of age. He had not finished high school and had held only one job in his life, and that for less than one year. His family regarded him as withdrawn and "different."

Several of the group, Patients E and F, had made suicidal gestures, and one, Patient F, had made four homicidal attempts against his parents. He had escaped from a maximum security ward in a hospital in another state and was brought to our hospital by the police. During the course of 12 years of illness he had been hospitalized innumerable times and had had 14 months of intensive psychotherapy in the Menninger Clinic.

Patients A and B had both been known to be autistic since childhood; they had made poor work adjustments and had no marital experiences. Patient B had never worked and had served innumerable jail sentences for vagrancy, usually being arrested while eating out of garbage cans and sleeping behind buildings.

Patients C and G were of the athletic type of body build and perhaps had the best premorbid adjustment of the group. However, Patient C had always been regarded by his family as shy and withdrawn and had not been capable of forming

a single friendship. Patient G was the only one of the group who had been married, and after 18 months of marriage had not completed a sexual union.

Patient D had been hospitalized on several occasions and had received somatic therapy at least three times. He had also received chemotherapy and group psychotherapy, none of which caused any perceptible change. He, too, had a poor premorbid adjustment and had consistently lacked significant interpersonal relationships.

D. Clinical Procedures

1. *Observation Chart.*—It seemed possible that the treatment period was too short for the discernment of psychological changes by classical methods. With this thought in mind, a daily observation chart was developed, which consisted of five sections plus "comment." Parts I (appearance: neat or careless), III (general mode of behavior), and V (affect: flat, exaggerated; appropriate, inappropriate) offered a framework for assessing objectively observable behavior that required no interaction between observer and patients. Parts II (quality and content of speech: none, initiates, responds, bizarre) and IV (trends of thought) served the purpose of helping to categorize responses of the patients to a given interpersonal situation. The purpose of this method was to permit simultaneous and standardized recording of changes occurring at the affect and thinking level and to furnish a basis for the evaluation of behavioral changes in as objective a manner as possible. Two observers worked independently and did not exchange information for the duration of the experiment. The observations were made at various times of the day and under sundry conditions.

2. *Psychological and Psychiatric Tests.*—For the purpose of complementing the daily clinical observations, the Minnesota Multiphasic Personality Inventory (MMPI) and the Multidimensional Scale for Rating Psychiatric Patients (MSRPP) were administered to each patient. In this way we were able to satisfy our curiosity concerning the suitability of classical clinical test procedures used at short intervals for evaluating changes in patient behavior. We think that both instruments served our purposes to a limited degree.

For the MMPI we deviated from the conventional manner by accepting a forced choice method in order to eliminate the "cannot say" category. This was deemed necessary when dealing with highly ambivalent patients, because at the time of the retesting any occurring changes would be more clearly delineated. In view of the size of our patient population, only small-sample statistical methods were applied for analyzing these data. T-scores and standard error of measurement for a score technique were adopted in the evaluation of the test material.

The MSRPP was handled in a similar way.[16] One of the observers evaluated the psychiatric section, while specially trained and experienced nurses worked over the nursing section. The second evaluation was done without reference to the initial one to avoid prejudicing the results. Individual scales considered pertinent to this experiment were inspected closely. With this instrument we explored the occurrence of common areas of change thought clinically to be similar. The scales were then further analyzed for the group as a whole to determine which changes occurred in common to the greatest number of patients.

E. Biochemical Methods

The excretion of 5-hydroxyindoleacetic acid (HIAA) was determined by the method of Udenfriend et al.[17] The tryptophan-load test (TLT) was carried out by administering 0.25 mM. of L-tryptophan after emptying the urinary bladder and by collecting the urine 2.5 and 5 hours after the intake of tryptophan. The urine was kept frozen at −15 C if the chemical analysis could not be carried out immediately.

Results

A. Daily Clinical Observations.—Between 10 and 11 days after the initiation of treatment Patients B, D, E, and G showed energy and activity not previously seen. On the 19th day Patient A became markedly aggressive and demanding, while on the 21st day Patient C lost interest in delusions of illness and displayed more interest in his external environment. Patient F exhibited seemingly appropriate affect one day later.

These four patients, B, D, E, and G, exhibiting behavioral changes within 11 days of treatment, were the most withdrawn, lethargic, and uncommunicative, and Patients B, D, and G had been mute for various periods of time up to 9 months. On the other hand, Patients C and F had always appeared to have adequate, though misdirected, energy at their disposal. These men were the last of the group to manifest any alteration in behavior and consistently responded less than the rest of the patients to the treatment. The changes which the

patients seem to have in common were primarily at a nonverbal, "kinetic" affect level, and were not accompanied by any striking trend of alterations in the thinking disorder.

The analysis of the behavioral observations revealed four distinctly recognizable phases, which appeared to be progressive steps of one unfolding process. These behavioral phases were delineated for the sake of clarity; in many instances it was difficult to draw a line between them because they often overlapped or occurred simultaneously.

Phase 1: The first noticeable difference in behavior among five of the patients consisted in a rise of the available energy level. At first this energy was diffuse and resulted in increased restlessness, pacing, posturing, and a greater display of schizophrenic mannerisms. Patients A, D, and E, who were among the most withdrawn, left their customary supine or fetal positions on the dayroom chairs and lounges and began to sit upright and move about. Perhaps the most striking characteristic of this phase was the new tonicity of postural adjustment. At this time it is not possible to know whether this change was simply an expression of a diffuse increase in physical energy, or whether it reflected a greater awareness of self or the external environment. Patients C and F did not exhibit a discernible change of this type. As previously mentioned, these two men had always had sufficient energy available.

Phase 2: Increased motor activity compatible with rising anxiety and tension appeared to grow from the previously described phase. For some of the patients, especially A and G, the transition was fast. Patient G was one of the first to verbalize feelings of being tense, which he described as "nervousness." Ward activities were either shared more or rejected more definitely than usual. The patients reacted toward other facets of hospital life with negativism and argumentativeness. The nursing service described them as being tense, edgy, and explosive. Apparently at this point sufficient energy had been mobilized so that all of the patients were actively experiencing anxiety. Possibly their former adjustment of passive withdrawal was no longer compatible with the current level of energy. As an example, we mentioned Patient A, who, in contrast with his previous behavior, was no longer able to withdraw behind newspapers or books. He began to refuse medication and complained about lack of treatment and requested to sign out of the hospital against medical advice. All of the other patients showed a similar behavior during the second to the third week of the treatment period, though not in such a marked degree as Patient A.

Phase 3: Soon after the increased anxiety appeared, these patients began seeking the support, or at least the company, of various members of the hospital personnel. This category of behavior also seemed to expand and grow out of the preceding phase. While this behavioral phase appeared at varied time intervals for each patient, it was observable in most of the patients during the third and fourth weeks of the treatment period. For some the need for human contact was noted, as in the cases of Patients A, C, and F. In Patients C and F this behavior occurred earlier than in any other group member, perhaps because they were originally less withdrawn. At about this time we began to notice an apparent sibling rivalry for the exclusive attention of staff members, and jealousy over attention given to other patients in the ward began to develop. Also at this time Patient D, who had previously curled up in a fetal position, began to watch for the observers to come to the ward. He began to smile before they came up to him. Once he even tried to initiate a conversation with one observer. This behavior is particularly interesting because this patient had never spoken or responded to either observer for periods of 7 and 12 months, respectively. Patient A not only initiated conversation with the observers, but also would monopolize the ward nurse for an hour at a time if permitted to

do so. Patient E previously seemed not to be aware of anyone, but now he began to address the ward nurse by name and demanded special attention from her. During this period six of the seven patients were starting conversations and were occasionally manifesting signs of humor, as well as displeasure and depression.

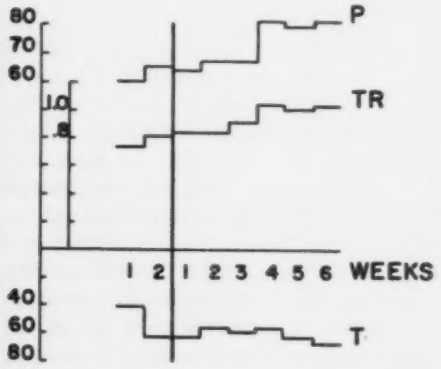
Phase 4: This behavioral phase is difficult to describe and shows overlapping with the previous steps. At various times during the experiment several of the patients were capable of responding in a manner appropriate to their feelings. However, we do not mean to imply that their feelings were appropriate to the reality situation at all times. We do intimate, however, that there was an increase in the expression of feelings that came into the patients' awareness. In some patients there was a decrease in ambivalence, and in others their new awareness of feelings appeared to increase their ambivalence and anxiety to the point of disorganization. It seemed to the observers that each patient at some time following the third week of treatment was able to display what is commonly called "appropriate behavior." However, for all except one, Patient G, this was a transitory experience and seemed to be a prelude to the eruption of an acute psychotic episode. The patients were beginning to show signs of shifting from withdrawn, lethargic schizophrenics to acutely anxious and active schizophrenics. Apparently, the flooding of the patient with anxiety released by the rapid infusion of affect was overwhelming to the personality, which had previously adjusted into a withdrawn psychotic state. The one patient who maintained his appropriateness and integration was Patient G, who probably had the most adequate premorbid character structure of all the patients in this particular group.

B. Psychological and Psychiatric Tests.—The results of this type of evaluation agreed remarkably with our behavioral observations. The analysis of the scales revealed an *increase* in motor activity, speech, denial of hallucinations, harmony of thoughts and feelings, and eating, while a *decrease* of cooperativeness and concern with bodily functions was observed. The alterations, however, were not uniform, not even in those patients who displayed similar behavior. Not a single case was recorded in which the entire group displayed changes for any one of the 62 scales. For three scales six patients evidenced changes, but the directions of these alterations were not identical. The same was true for 11 scales, where five patients exhibited changes.

One patient, F, was unable to take the second test, owing to increased anxiety and aggressiveness. For this reason the group had to be reduced to six for the statistical analysis of the test data. The first statistical procedure applied to these data was a series of scores, one for each of the nine clinical scales and for each of the three validity scales. The application of this method was attempted in order to utilize the group data. No significant *t*-values were obtained by this method. Thus it must be concluded that no uniformly significant changes for the group as a whole took place. The data were analyzed again for each individual. For this treatment of the data the standard error of measurement for a score technique was employed. The results of this procedure revealed that, with one exception (Patient C), all subjects manifested some significant shifts between the first and the second administration of the test. No changes were accepted unless they fell at the 0.01 or 0.05 level of confidence. One patient, F, showed significant alterations on each of the clinical scales at the 0.01 level of confidence. In his case all of the shifts indicated a decrease in pathology. Two other patients, B and D, either displayed no change or showed significant alterations in the direction of increased pathology. Only three of the scales revealed a shift in behavior by four or more patients, and these were the depression, the masculine-feminine, and the schizophrenia scales. On the depression scale, two patients manifested alterations at the 0.01 level of confidence, and three, at the 0.05 level. The sixth pa-

tient, C, also showed an insignificant tendency to change. On the M-F scale, again, for five out of six patients significant shifts occurred, two at the 0.01 level and three at the 0.05 level of confidence. On the schizophrenia scale, four out of six showed significant alterations, all at the 0.01 level of confidence.

In spite of the limitations of the statistical analysis of individual cases, these data are included because it became clear that they substantiated the behavioral observations presented above. Like the other tools used for clinical evaluation, the test results indicate that there was a mood change in these patients, and, furthermore, a tendency toward more irritability and aggressiveness and less withdrawal. However, intensity and direction of changes were not uniform. For example, on the depression scale, Patients B and D showed an increase of depression, while others displayed a decrease. Again, on the M-F scale, Patients B and D manifested a shift toward more femininity, while the others moved toward the more masculine. Of those four who changed on the schizophrenia scale, only one patient, D, presented an increased pathology, while the other three showed less. One general trend became apparent, namely, the shift toward acute psychosis, even though it was not statistically demonstrated.



Daily consumption of protein (*P*) and tryptophan (*TR*), in grams. Average temperature in Chicago (*T*), in degrees (F). Vertical line indicates start of the experimental period.

TABLE 1.—*Protein and Tryptophan Intake During Experimental Period* *

	Preexperimental	Experimental	*P*
Protein	65±14	81±8	<0.03
Tryptophan	0.81±0.18	1.02±0.07	<0.03

* The figures indicate the averages for seven patients for the week preceding the experimental period and the sixth week of the experimental period. The daily consumption of protein and tryptophan, in grams, was averaged for one week.

C. Dietary Protein and Tryptophan Intake.—As the experimental period continued, it was noted that the intake of protein, and consequently tryptophan, increased during the third or fourth week after initiating the drug regimen and stabilized itself at this new level. This increase in dietary protein was accounted for principally by an augmented milk consumption. Since the experimental period occurred during the late spring months, this increase in consumption could have reflected increased fluid intake due to rising environmental temperatures. However, the data for the mean temperature during that period (Figure) indicates that the increased milk consumption, and, consequently, protein intake, is due to a factor apart from the ambient temperature. The data on protein and tryptophan consumption are shown in Table 1.

D. 5-Hydroxyindoleacetic Acid Excretion.

The daily excretion of 5-HIAA for the seven patients on experiment dropped from the preexperimental value of 3.5 mg. per day to 2.4 mg. per day on the 12th day after administration of iproniazid and tryptophan (Table 2). This diminished 5-HIAA excretion remained fairly constant

TABLE 2.—*Daily Excretion of 5-Hydroxyindoleacetic Acid* *

Time		5-HIAA	
Consecutive Days	Day of Period	Mg/Day	*P*
1	I: 1	3.5±0.83	
15	II: 4	3.1±1.48	0.50
23	12	2.4±1.12	0.06
30	19	2.3±1.29	0.06
37	26	2.7±1.69	0.26
44	33	2.5±1.12	0.08
51	40	1.8±1.17	0.01
56	III: 2	2.9±1.61	0.46

* The values indicate the amount excreted in 24 hours as determined in 24-hour specimens. Period I: preexperimental; Period II: experimental; Period III: postexperimental. The *P* value is calculated by comparison of each period with Period I.

TABLE 3.—*Urinary Excretion of 5-Hydroxyiodoacetic Acid (5-HIAA) After Administration of Tryptophan* **

Period †	Basal 1		2		3			t	P
	Volume, Ml.	5-HIAA, Mg.	Volume, Ml.	5-HIAA, Mg.	Volume, Ml.	5-HIAA, Mg.			
Controls (17)	136	0.35	141	0.71	144	0.78	(1) vs. (2)	3.27	<0.01
							(1) vs. (3)	3.45	<0.01
Schizophrenics (26)	148	0.32	134	0.33	170	0.25	(1) vs. (2)	0.10	>0.9
							(1) vs. (3)	0.16	>0.9
Controls vs. schizophrenics									
t		0.13		3.69		4.81			
P		>0.9		<0.01		<0.01			

* Dose of tryptophan, 0.1 mM. per kilogram of body weight.
† Basal period, before tryptophan administration; 2, period from 0-2.5 hours after tryptophan administration; 3, period from 2.5-5 hours after tryptophan administration.

until the 40th experimental day, when a further decline, to 1.8 mg/day, was evidenced. At cessation of the drug regimen the 5-HIAA excretion rose immediately to 2.9 mg. per day. These data indicate that the response to iproniazid administration could be detected by a diminution in 5-HIAA output, indicative of a reduced metabolism of serotonin, and that this effect is quickly reversible, under these experimental conditions, by termination of drug administration.

The results obtained after the intake of one dose of a large amount of L-tryptophan to 26 schizophrenic patients and 17 controls, neither group receiving iproniazid, are shown in Table 3. While the basal values obtained do not represent exactly the fixed time period that the subsequent two periods do, they are for the specimen collected at about 9:30 a. m., after voiding of the urine, and represent an approximation. However, the urinary volumes collected are shown to demonstrate that these values represent approximately equal volumes of urine in all periods.

Statistical analysis of the results indicate that the excretion of 5-HIAA in normals is significantly higher after a test dose of L-tryptophan is administered, while schizophrenic patients do not respond to the L-tryptophan in this manner.

Comment

The data presented appear to demonstrate that clinically observable behavioral changes occurred in the patient population on a combined iproniazid and tryptophan regimen. These changes were observed about two weeks after the experiment was initiated, and, while the efficacy of the combined drugs, as contrasted with that of the iproniazid, is difficult to evaluate, comparison with reports in the literature indicate some advantage in this procedure. Thus, in studying iproniazid alone, Kamman, Freeman, and Lucero [18] reported some improvement only in a second eight-week period. In another investigation, in 7 out of 13 schizophrenics no effect was observed after five weeks of treatment.[8] The discrepancies in results noted by these investigators could be due to other factors in the experiment, but certainly the simultaneous administration of tryptophan in this work cannot be discounted as a major variable in producing the relatively rapid changes, as compared with the slower behavioral changes observed when tryptophan was omitted.

The biochemical observations indicate that iproniazid did reduce the amount of 5-HIAA excreted. Whether the cerebral serotonin levels were increased can only be inferred from these data and from animal experimentation. A more crucial problem appears to be whether or not this presumptive increase in serotonin levels is causally related to the observed behavioral changes. It should be pointed out that iproniazid will inhibit other enzymes and that monoamine oxidase can act on amines other than sero-

tonin.[19] The action of the drug thus may be mediated through some other metabolite.

If cerebral serotonin is involved in the maintenance of normal nerve function, some interesting ideas emerge. Serotonin has been found to be localized in the brain, principally in the hypothalamic area, the midbrain reticular formation, and components of the rhinencephalon, such as the hippocampus, amygdala, and septal region.[20,21] These are the "subcortical structures regarded as parts of the anatomic substrate of emotion." [22] Since alterations of affect commonly occur in behavioral disturbances, it can be seen that abnormal metabolic events in these anatomical areas could be correlated with changes in affect. Since serotonin is concentrated in these areas, and if one assumes a purposeful function for such localization, it might be assumed that disturbances in serotonin metabolism could result in alteration of affect. This is reducing the observations to its simplest terms, since, as discussed, the action of monoamine oxidase may well encompass other physiologically active amines, and, also, iproniazid may affect other enzyme systems which may have a crucial role in the maintenance of normal function.

The results obtained on the tryptophan-load test (TLT) would indicate that the patients did not respond to the tryptophan in terms of 5-HIAA excretion as did the controls. It has been shown in dogs that feeding tryptophan will produce an increased urinary 5-HIAA excretion.[23] However, in addition to the psychoses, many other differences existed between our patient and control groups (nutritional status, degree of activity, dietary habits), so that it is conceivable that other variables may be factors in producing the results obtained. Despite these limitations, the differences in the metabolism of tryptophan between the two groups is of interest, since it has been shown that schizophrenia is associated with an abnormal metabolism of aromatic amino acids.[24-27] Because of the limitations of the experimental design, it is not possible to discuss the therapeutic implications of these results. However, it is apparent that it seems possible in some schizophrenic patients to alter some aspect of the brain metabolism and thereby alter behavior patterns. In view of the data presented, it is evident that clinically observable behavioral changes occurred in the patient population during the study. These changes consist of (1) an increased energy level, (2) increased motor activity compatible with rising anxiety and tension, (3) awakening of the ability to accept interpersonal relationships, and (4) voluntary selection of higher protein and tryptophan diet. These clinical changes are viewed as worthy of further study to determine whether they constitute a more favorable milieu for other forms of treatment, including psychotherapy.

Summary

Seven schizophrenic patients were given iproniazid and L-tryptophan for a period of six weeks.

During the experimental period, the patients exhibited an increase in energy level and motor activity and improvement in the ability to accept interpersonal relationships, and displayed more affect. In addition, their voluntary intake of protein and tryptophan increased. These changes became apparent about two weeks after the initiation of the experimental period.

During the course of the experiment the 5-hydroxyindoleacetic acid excretion per 24 hours diminished. This low excretion was rapidly reversible after the cessation of drug administration.

In a tryptophan-load test 26 schizophrenic patients did not exhibit any increase in 5-hydroxyindoleacetic acid excretion over the basal level after tryptophan administration, while 17 controls showed an 100% increase in the excretion of this compound. No difference between the two groups at the basal level was observed.

Some implications of the results obtained in relation to serotonin metabolism are discussed.

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Books

BOOK REVIEWS

Autonomic Imbalance and the Hypothalamus. By Ernst Gellhorn, M.D., Ph.D. Price, $8.50. Pp. 300. University of Minnesota Press, 10 Nicholson Hall, Minneapolis 14, 1957.

The avowed purpose of this monograph by Dr. Gellhorn, Professor of Neurophysiology at the University of Minnesota, is to define the theoretical significance of the clinical observations of Funkenstein on the methacholine (Mecholyl) test in neuropsychiatric patients.

The first two hundred pages of the volume are concerned with experimental evidence relating principally to the establishment of three concepts. The first is that the central reactivity of the autonomic system can be altered reflexly by means of an initial stimulus, and that this alteration can be detected by means of a test stimulus. "Reactivity" of the autonomic system is measured principally by the triumvirate of blood pressure, pulse rate, and nictitating-membrane contraction in the cat. It is shown, for example, that during acetylcholine- or histamine-induced hypotension (initial, or "tuning," stimulus), posterior hypothalamic stimulation (test stimulus) is more effective in producing sympathetic responses than during normotension. Sinoaortic denervation blocked this effect. In Gellhorn's terminology, the autonomic centers have been "tuned" toward a state of sympathetic reactivity resulting in an "autonomic imbalance." The second major point made in the monograph is that an autonomic imbalance, as defined by alteration of the measured response to a test stimulus, can be produced by decreasing or increasing excitability in the anterior or posterior hypothalamus by means of localized lesions or pentylenetetrazol U. S. P. (Metrazol) or thiopental (Pentothal) injection. The third major concept developed is that increased hypothalamic activity increases cortical activity, the hypothalamic-cortical discharge varying inversely with blood pressure at the arterial pressor receptors. The system has a positive feedback such that increases in cortical activity increase hypothalamic activity.

Once the author has defined "autonomic imbalance" and has established that it can originate in the hypothalamus and that there are connections between hypothalamus and cortex, the groundwork has been laid for the clinical applications, discussed in the remaining sixty or so pages. Various "psychosomatic" disorders are discussed cursorily as clinical examples of autonomic imbalance. The methacholine and arterenol (norepinephrine) tests in man are next discussed. On the basis of the animal work, the area of methacholine-induced hypotension is regarded as an inverse indicator of central sympathetic excitability, whereas arterenol-induced bradycardia is an indicator of parasympathetic reactivity. Sympathetic and parasympathetic reactivity is shown to decrease in the human with age. Patients with neuropsychiatric disorders show more hypo- and hyperreactors of the sympathetic system than do normals, as well as lower reactivity of the parasympathetic system.

The major step in the argument follows. *Since* alterations in hypothalamic excitability were shown to alter autonomic reactivity (under experimental situations), *therefore* clinical alterations in autonomic reactivity are reflections of altered hypothalamic functions! Since the hypothalamus and the cortex are connected, the way is clear for the suggestion that therapy in mental illness be partly directed toward restoration of autonomic disturbances. A direct quotation of the final argument follows.

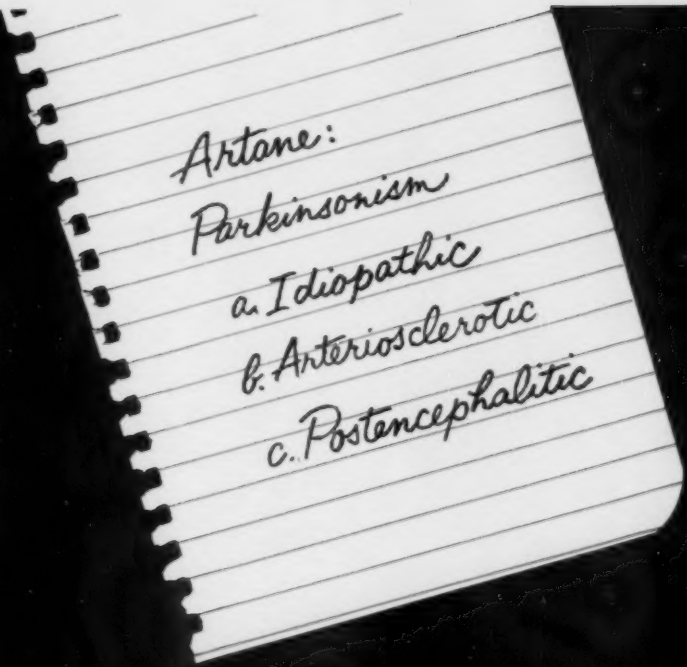
"The experimental work and the clinical tests described in this monograph indicate that the autonomic excitability of the hypothalamus can be measured in man and that hypothalamic autonomic disorders and imbalances can be ascertained in certain forms of mental illness. The parallelism between the clinical recovery and the Funkenstein test suggests that autonomic hypothalamic disturbances are not a by-product but intimately related to the behavioral disturbance. The therapy, therefore, should be directed toward a restitution of the autonomic balance. Cases characterized by central sympathetic hyperfunction require a form of therapy diametrically opposed to that needed for cases of parasympathetic hyperfunction or sympathetic hypofunction. . . . It is not assumed that the abnormal behavior observed in mental illness is the immediate effect of the disturbed hypothalamic functions that may be revealed by autonomic tests. But alterations in hypothalamic functions and autonomic imbalance, it is thought,

lead secondarily to changes in the hypothalamic-cortical discharge and thereby to alterations in cortical functions. Even if this factor is admitted to be only one of the many (as yet unknown) productive of the behavior disturbances seen in functional psychoses, the restoration of the hypothalamic balance and of the hypothalamic-cortical discharge may constitute the turning point in the complex processes of disease. All medical therapy, it should be remembered, is based on the faith that nature, if given a chance, will lead to improvment and, within certain limits, to recuperation."

Since the book is so clearly separated by the author into two parts, it is an overwhelming temptation to evaluate the experimental and clinical sections separately. The first section is characterized by page after page of experimental protocols and data records. It is easy to see why Dr. Gellhorn, in the preface, advises "readers who are not well acquainted with neurophysiological research or cannot spare the time to read the detailed report of the physiological experiments" to skip material, amounting to 50% of the monograph, and to substitute for it summary pages in the latter part of the volume. Much of the experimental material is repetitious and not always contributory to the main stream of thought. The interpretive material at the end of the chapters would have been more valuable if summarizing diagrams had been used instead of verbal description. However, ease of reading aside, the experimental evidence is quit convincing that sympathetic and parasympathetic reactivity is altered by a number of peripheral stimuli and also by the excitability of hypothalamic structures. (At least there are stimulation and ablation procedures described as taking place in the hypothalamus, although only one such experiment is accompanied by pictures of brain sections.) Gellhorn makes quite obvious the underlying continuity between the autonomic and the somatic central nervous system, certainly a contribution to psychosomatic medicine.

With the exception of the material using methacholine and arterenol in human subjects (described above), the clinical application of the experimental material goes far beyond the data into almost pure speculation. No evidence is shown that autonomic imbalance *necessarily* results from hypothalamic disturbance, surely a crucial point in the whole final section. Gellhorn himself points out that in applying the experimental data to clinical problems he has "trodden on dangerous ground." It is possible, of course, that the speculation will prove to be fact, in which case a valuable contribution to the physiology of mental illness will have been made. If not, then the author's final statement may be correct: "It is sufficient to have attempted great things."

NEENA B. SCHWARTZ, Ph.D.



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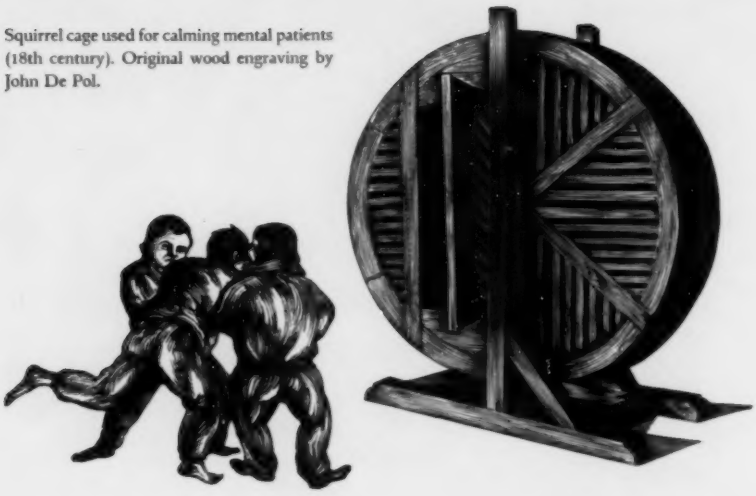
Squirrel cage used for calming mental patients (18th century). Original wood engraving by John De Pol.



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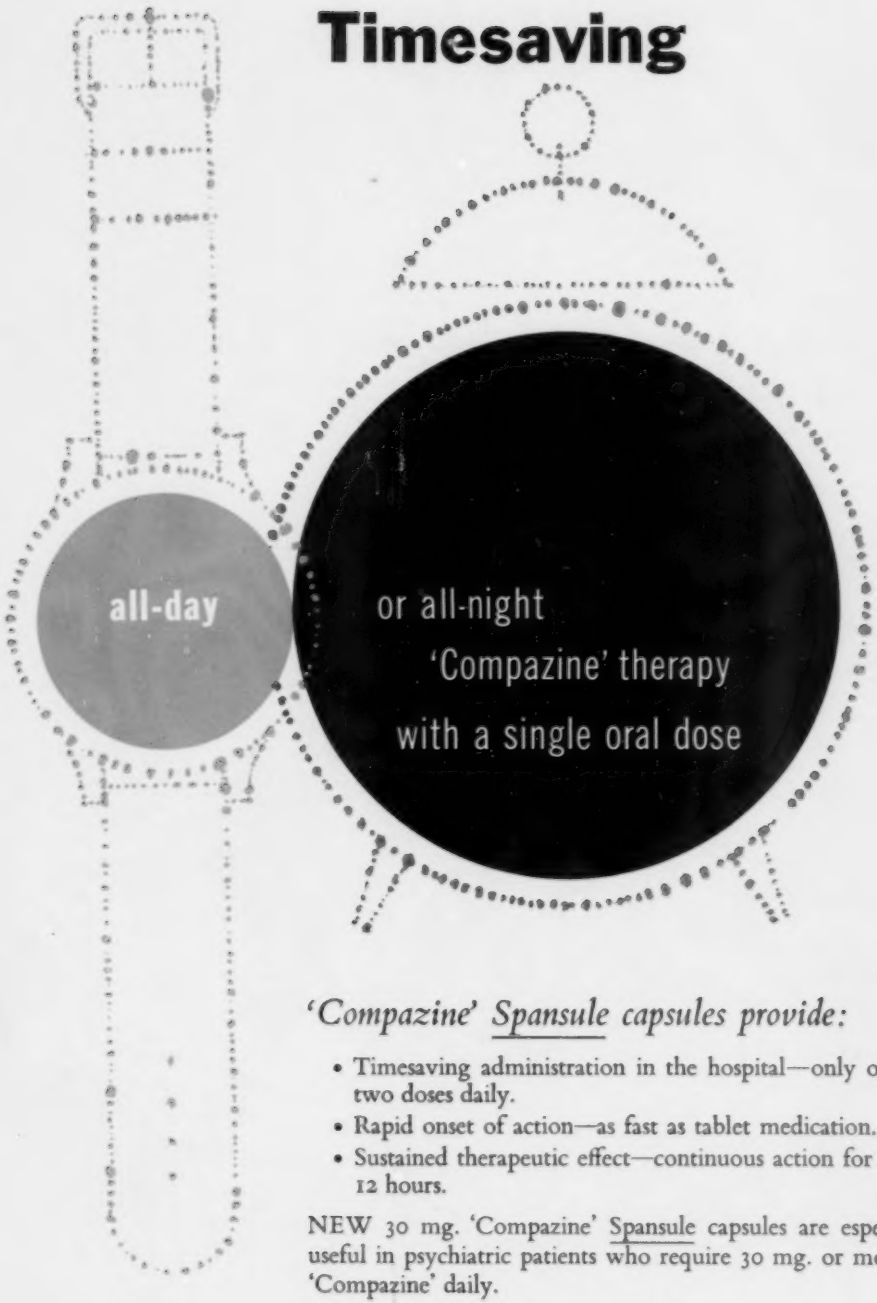

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